

FINAL
SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:
HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV Uninfected Cisgender Men and Transgender Women who have Sex with Men, Version 1.0, February 2, 2016

DAIDS Document ID: 20725

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 2.0
July 25, 2018

IND #122,744

Information/Instructions to the Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the HPTN 083 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as required as soon as possible for review and approval. This amendment impacts the study informed consent forms (ICFs); all study sites must prepare updated informed consent forms and obtain IRB/EC approval of the updated forms. Approval also must be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this amendment, using site-specific Version 2.0 ICFs when obtaining informed consent under protocol Version 2.0. Re-consent for specimen storage and future research, genetic testing, and the DXA subset (where applicable) is not required.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this amendment.

This Summary of Changes, Protocol Version 2.0, corresponding site-specific informed consent forms, and all associated IRB/EC and regulatory entity correspondence should be retained in each site's essential document files for HPTN 083.

The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration (FDA) for inclusion in Investigational New Drug application (IND) #122,744.

Summary of Revisions and Rationale

The modifications included in this protocol amendment and the rationale are summarized below and detailed in the ‘implementation’ section that follows. The modifications are presented generally in order of their appearance in the study protocol. The major items included in this protocol amendment are as follows:

1. The content of Letter of Amendment #1, May 24, 2016; Letter of Amendment #2, July 26, 2016; Letter of Amendment #3, November 10, 2016; Clarification Memo #2, October 19, 2017; and Letter of Amendment #4, December 14, 2017, are included. Clarification Memo #1 changes are not included because Clarification Memo #2 supersedes it. The rationale for each item included in these documents is not repeated below (refer to the respective final document for each); however, the modifications are included in this document under the “implementation” section.

The following revisions are new to Version 2.0; that is, they do not appear in the letters of amendment and clarification memos listed above:

2. The Title Page, footer, and Protocol Signature Page are updated to reflect the new version number and date.
3. The Table of Contents is updated to reflect the new version.
4. The Protocol Team Roster is updated to reflect current membership and contact information.
5. The Schema is updated as follows:
 - a. The Study Duration section is updated for participants who prematurely transition out of Step 1 or Step 2. If a participant is in Step 1 and does not transition to Step 2, he or she will be followed at annual visits until all participants complete Step 2. If a participant is in Step 2 and prematurely transitions to Step 3, he or she will complete Step 3 and then transition to annual visits until all participants complete Step 2. This type of follow-up is required to meet the principles of the intent-to-treat primary statistical analysis of the study.
 - b. The Study Regimen sections is updated for participants who prematurely transition out of Step 1 or Step 2. If a participant is in Step 1 and does not transition to Step 2, he or she will be followed at annual visits until all participants complete Step 2. If a participant is in Step 2 and prematurely transitions to Step 3, he or she will complete Step 3 and then transition to annual visits until all participants complete Step 2. This type of follow-up is required to meet the principles of the intent-to-treat primary statistical analysis of the study.
 - c. India has been removed as a country with sites participating in the study.

6. Section 1.2.1 is updated to include additional findings from non-human primate studies of CAB LA.
7. Section 1.3.2 is updated to correct reference #80 to reference #85 (but is not depicted in the modifications section below). This section is also updated to include additional findings from a phase 2a study of CAB LA.
8. Section 1.4 is updated with the latest available clinical data from ongoing and completed CAB trials.
9. Table 2 is updated with the latest available clinical data from ongoing and completed CAB trials.
10. Section 1.4.1 is updated with the latest available clinical data from ongoing and completed CAB trials.
11. Section 2.3 is updated to remove India as a country with sites participating in the study.
12. Section 2.5 is updated for participants who prematurely transition out of Step 1 or Step 2. If a participant is in Step 1 and does not transition to Step 2, he or she will be followed at annual visits until all participants complete Step 2. If a participant is in Step 2 and prematurely transitions to Step 3, he or she will complete Step 3 and then transition to annual visits until all participants complete Step 2. This type of follow-up is required to meet the principles of the intent-to-treat primary statistical analysis of the study.
13. Section 3.1 is updated to specify that sex at birth should be used for calculated creatinine clearance. A note is added regarding enrolling participants with a calculated creatinine clearance between 60 and 70 mL/minute, as limited changes to creatinine clearance during the course of the study may lead to protocol-mandated study-product holds. This section is also updated to clarify that the inclusion criterion of “no grade 3 abnormal laboratory values at screening” includes all laboratory test results acquired at the screening visit and is not limited to protocol-required test results.
14. Section 3.4 is updated to clarify participant co-enrollment to another study of any design is not allowed.
15. Section 3.6 is updated to state that formal participant withdrawal will only occur in the case of withdrawal of consent, death, extreme/unusual circumstances to protect participant safety, or the participant is unwilling or unable to comply with the study procedures, and that participants should not be terminated for safety-related reasons unless approved by study leadership and the sponsor. Terminations should be rare in general due to the requirements of intent-to-treat primary statistical analysis of the study.
16. Section 4.2.1 is updated to clarify storage temperature of active and placebo oral CAB tablets.
17. Section 4.2.2 is updated to clarify storage temperature of injectable CAB LA.

18. Section 4.6 is a new section added to recommend quantity of oral study products to be dispensed to participants during Step 1 and Step 2 of the study.
19. Section 5.2 is updated to specify the procedures for the BMD subset, including the target window for the baseline DXA scan.
20. Section 5.3 is updated to remove the requirement to contact the CMC regarding the adherence rate to oral study product during Step 1, and states that participants with pill counts identified to represent less than 50% of dosing on elapsed days between study entry and the Week 4 visit, as assessed by pill count at the Week 4 visit, will not be allowed to transition to Step 2. Participants in this case will be asked to attend annual visits until all participants complete Step 2 of the study (which is required to meet the principles of the intent-to-treat primary statistical analysis of the study). Language is also added to refer the reader to the Study-Specific Procedures Manual (SSP) for instructions regarding participants who forget to bring their pills to the Week 4 visit. Additionally, the words “HIV testing” are removed from the description of annual visits since the requirements for the annual visits include other procedures in addition to HIV testing.
21. Section 5.4 is updated to add a “Note 2” that directs the reader to consult the Study Specific Procedures (SSP) Manual regarding split or merged visits. These types of visits were not anticipated when the study was first implemented, and have now occurred with sufficient frequency to require specific standardized direction in the SSP for each circumstance.
22. Section 5.6 is updated as follows:
 - a. Procedures for the BMD subset are specified, including the target window for the two follow-up DXA scans.
 - b. An identical change in Section 5.6 to the change noted in item #21 (above) for Section 5.4.
23. Section 5.9 is updated to specify a target visit window for the DXA subset. Additionally, it is updated to remove the requirement to contact the CMC for out of target window injection visits that are a minimum of **6 weeks** from the last injection and a maximum of **15 weeks** from the prior injection. It also specifies that it is required to contact the CMC for guidance in cases outside of these parameters.
24. Section 5.11 is updated to remove “HIV testing” from the description of annual visits since the requirements for the annual visits include other procedures in addition to HIV testing.
25. Section 5.12.1 is a new section regarding emergency unblinding procedures in the very rare and life-threatening event where the Investigator or Record believes unblinding is necessary for immediate proper medical management of the participant.
26. Section 5.14 is updated to clarify communication guidelines to the CMC for notification of any positive/reactive laboratory testing for syphilis. Additionally, it is updated to allow study funding to be used to support symptomatic testing for sexually transmitted infections (STIs). It also specifies that STIs will be reported into the study database via the adverse event electronic log as well as the STI electronic case report form.

27. Section 5.15 is updated to clarify that participants whose screening tests for Hepatitis B and C are inconclusive will not be allowed to enter the study.
28. Section 5.17 references Section 3.6 of the protocol as the same language is included in that section and repeating it in Section 5.17 is unnecessary and redundant.
29. Section 6.3 is updated to state that STIs will be reported into the study database via the adverse event electronic log **as well as** the STI electronic case report form.
30. Section 6.4 is updated to correct the website address for DAIDS Regulatory Support Center (RSC).
31. Section 6.4.1 is updated to remove outdated EAE submission instructions as all sites are using DAERS for EAE reporting. The website address to obtain the DAIDS EAE form is corrected. DAIDS-approved language is also added.
32. Section 6.4.2 is updated to correctly place the statement “must be both in order to require expedited reporting”. DAIDS-approved language is also added.
33. Section 6.4.3 is updated to correct the website address to obtain the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.
34. Section 7.11.4 is updated to remove India as a country with sites participating in the study.
35. Section 10.3 is updated to remove reference to DataFax since MediData Rave is the electronic data management system utilized for this study.
36. Section 10.4 is updated to include inspection by additional regulatory authorities.
37. References #86 and #87 are added.
38. Appendix ID - Schedule of Procedures and Evaluations for Annual Visits - is updated to remove the words “HIV testing” from the title of the appendix as well as throughout the body of the appendix since the requirements for annual visits include other procedures in addition to HIV testing.
39. Appendix III – Toxicity Management – is updated as follows:
 - a. The General Guidance section is updated in the first paragraph to specify that individual cases of emergency unblinding may also occur under certain rare medical circumstances. The second paragraph is updated to clarify that general guidance refers to all AEs except for ALT, creatinine clearance (absolute and change from baseline), and CPK and that the corresponding toxicity management tables should be used for each of these. The general guidance for Grade 3 and 4 AEs is updated to clarify that a Grade 3 or 4 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing. This language previously appeared under the ALT section found in - Guidance on Toxicity Management for Specified Toxicities- and is moved to the general guidance section where it belongs.

- b. The General Criteria for Discontinuation of Study Product section is updated to remove the words “HIV testing” from the description of annual visits since the requirements for the annual visits include other procedures in addition to HIV testing.
- c. The ALT guidance under - Guidance on Toxicity Management for Specified Toxicities – is updated to move language erroneously included to under general guidance (refer to item 37a above), as well as to move language regarding permanent discontinuation to the injection phase guidance in the ALT section; language is added to that guidance to state that participants who prematurely transition to Step 3 and then complete Step 3 will then transition to annual visits until the blinded portion of the study is complete for all participants (which is required to meet the principles of the intent-to-treat primary statistical analysis of the study). Language is also updated to remove “HIV testing” from the description of annual visits since the requirements for the annual visits include other procedures in addition to HIV testing.
- d. The Creatinine Clearance guidance under – Guidance on Toxicity Management for Specified Toxicities – is updated to add a NOTE above the table clarifying that clinical management of Grade 3 and 4 changes in creatinine clearance should follow the “Toxicity Management General Guidance” only when the absolute creatinine clearance is < 90 mL/min. The reason for this change is that the protocol is limiting CMC adjudication to only clinically relevant changes in creatinine clearance. In addition, the statement in the first row, last column “for adjudication and recommendation for further testing and follow-up” has been added to be consistent with the same instructions in the other rows.
- e. The Creatine Phosphokinase (CK or CPK) guidance under – Guidance on Toxicity Management for Specified Toxicities - is updated to include guidance for Grade 1 and 2, add language to contact the CMC if Grade 3 still persists after retesting, remove unnecessary language under Grade 4 Study Product Use column and add minor clarifying language under the Follow-Up and Management column.

40. Appendix IV: Sample Screening and Enrollment Informed Consent Form (ICF)

- a. The first page of the consent is updated to reflect the new version number and date.
- b. Step 1: Enrollment Visit is updated to specify that a participant will be informed when enrollment to the DXA subset is no longer available, and that only sites that participated in the DXA subset should include this language in their local informed consent forms. The subset is currently closed; however, it may be necessary to open it again in case more participants are needed due to lost to follow-up in the original subset. This section is also updated to specify that the subset will consist of 350 participants and will include a dietary calcium assessment.
- c. Step 1: Weeks 2 and 4 Visits is updated to include a note about premature transition to Step 3 in the event of study product side effects or inadequate pill count measures. A minor text addition now identifies the corresponding section of the informed consent form as “Annual Visits” for further clarity.

- d. Step 3: Language is added to include collection of concomitant medication information and a note about blood collection for syphilis testing which was inadvertently omitted in the previous version.
 - e. Language is added per item 22 and 23 above regarding split injection visits and the possibility of additional blood required if such a visit is necessary.
 - f. Language is added to include premature transition to Step 3 due to inadequate oral adherence during Step 1, as well as to add collection of concomitant medication information during these annual visits which was inadvertently omitted in the previous version.
 - g. The signature page of the ICF is updated to reflect the new version number and date, and to include a signature block for a participant to acknowledge that he or she has been informed the DXA subset is no longer open to join.
41. In compliance with Electronic Common Technical Document (eCTD) requirements, all active hypertext links to external websites and email addresses have been deactivated. Hyperlinks have been created for all referenced Appendices, Sections and Tables when they are not located on the same page, also per eCTD requirements. Additionally, other minor editorial and typographical updates and corrections are also included throughout the full amendment.

Implementation of Modifications

Modifications of protocol text are described below. Modifications are generally listed in order of appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.

Title Page, footer, and Protocol Signature Page

- Updated to Version 2.0, dated July 25, 2018

Table of Contents

- Updated to reflect the contents of the new version

Protocol Team Roster

Added:

- Adeola Adeyeye MD, MPA (c), DAIDS Medical Officer, Prevention Sciences Program, Division of AIDS, NIAID, NIH (LoA #1, 24 May 2016)

- David Burns, MD, MPH, DAIDS Medical Officer, Division of AIDS, NIAID (LoA #1, 24 May 2016)
- Kailazarid Gomez-Feliciano, MPM, Senior Clinical Research Manager, FHI 360 (LoA #2, 26 Jul 2016)
- Brett Hanscom, PhD, HPTN SDMC, SCHARP-FHCRC (V2.0, 25 Jul 2018)
- María del Rosario Leon Rhandomy, Barranco/San Miguel CRS, IMPACTA (V2.0, 25 Jul 2018)
- Bijal Patel, Pharm. D., BCPS [c], Protocol Pharmacist, Division of AIDS/NIAID/NIH (LoA #2, 26 Jul 2016)
- Nittaya Phanuphak, MD, PhD, Chief, Prevention Department, Thai Red Cross AIDS Research Centre (LoA #1, 24 May 2016)
- Hyman M. Scott, MD MPH, Research Scientist, Bridge HIV/ San Francisco Department of Public Health (LoA #1, 24 May 2016)
- Katherine Shin, Pharm.D., Senior Pharmacist, Pharmaceutical Affairs Branch, Division of AIDS (LoA #4, 14 Dec 2017)
- Pich Seekaew, Thai Red Cross AIDS Research Centre (V2.0, 25 Jul 2018)
- Philip Sullivan, MPH, MLS (ASCP)^{CM}, HPTN Laboratory Center Lab QC/QA Coordinator (LoA #4, 14 Dec 2017)

Removed:

- Vanessa Elharrar, MD, MPH, DAIDS Medical Officer (LoA #1, 24 May 2016)
- Bijal Patel, Pharm. D., BCPS [c], Protocol Pharmacist, Division of AIDS/NIAID/NIH (LoA #4, 14 Dec 2017)
- Michelle Wildman, Pharm D, Protocol Pharmacist, Division of AIDS/NIAID/NIH (LoA #2, 26 Jul 2016)
- Cheryl Marcus, BSN, University of North Carolina at Chapel Hill (V2.0, 25 Jul 2018)

Contact information updated:

- Adeola Adeyeye MD, MPA (c), DAIDS Medical Officer, Prevention Sciences Program, Division of AIDS, NIAID, NIH (V2.0, 25 Jul 2018)
- David Burns, MD, MPH, DAIDS Medical Officer, Division of AIDS, NIAID (V2.0, 25 Jul 2018)
- Cheryl Blanchette, HPTN Leadership and Operations Center Community Programs Associate, FHI 360 (V2.0, 25 Jul 2018)
- Sheldon Fields, PhD, RN, FNP-BC, AACRN, FAANP, FNAP, FAAN, Dean and Professor, School of Health Professions, New York Institute of Technology (LoA #1, 24 May 2016; LoA #2, 26 Jul 2016; LoA #4, 14 Dec 2017)
- Tim Holtz, MD, MPH, Division of Global HIV and TB (LoA #2, 26 Jul 2016)
- Steve Safren, PhD, University of Miami and Fenway Health (LoA #4, 14 Dec 2017; V2.0, 25 Jul 2018)
- Katherine Shin, Pharm.D., Senior Pharmacist, Pharmaceutical Affairs Branch, Division of AIDS (V2.0, 25 Jul 2018)

Schema

REVISION #5a, V2.0, 25 Jul 2018:

- Note: The Study Duration section is impacted and included below.

Approximately 4.5 years total, with individual participants being followed between 1.5 years (for the latest enrolling participants) to 4.5 years (for the earliest enrolling participants). Accrual will require approximately 130 weeks. In Step 1, participants will receive oral tablets for 5 weeks. **Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will be asked to attend annual visits until all participants complete Step 2 of the study.** In Step 2, participants will receive injections (as a single injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral tablets. Step 2 will be continued until the required number endpoints is reached, estimated to be approximately when the final participant reaches 60 weeks on Step 2 (**study week 65 for the final participant**). Participants will be all simultaneously unblinded at the conclusion of Step 2. In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks. **Participants in Step 2 who prematurely transition to Step 3 will complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual visits until all participants in the study complete Step 2.** Participants will therefore be followed between 113 weeks to 233 weeks (between 65 and 185 weeks on blinded study medication and up to 48 weeks on open-label daily oral TDF/FTC ~~with or without annual follow-up~~). All participants will be transitioned to locally-available HIV prevention services, including services for PrEP, if available, at the end of their participation in the study, **or if they transition to annual visits in Step 1 or Step 2.**

LoA #4, 14 Dec 2017:

- Note: Only the second paragraph of Step 3 under Study Regimen is impacted and included below.

A participant with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of the ~~Clinical Management Committee (CMC)~~ 083HIV@hptn.org group.

REVISION #5b, V2.0, 25 Jul 2018:

- Note: The Study Regimen section is impacted and included below.

Once randomized to one of two arms, participants will move through the following steps (active drugs are shown in bold text):

Step 1:

Arm A – **Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for five weeks

Arm B – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for five weeks

A participant that becomes HIV-infected during Step 1 of the study will permanently discontinue study product and will be terminated from the study, and referred for HIV-

related care. **Additionally, participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will remain blinded to their study assignment and be asked to attend annual visits until all participants complete Step 2 of the study.**

Step 2:

Arm A – **CAB LA** (600 mg as a single intramuscular [IM] injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral TDF/FTC placebo.

Arm B – **Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and IM placebo at two time points 4 weeks apart and every 8 weeks thereafter (matching vehicle, identical volume as active injectable product in Arm A).

This step will continue until the required number of endpoints is reached.

A participant that becomes HIV-infected during Step 2 of the study will permanently discontinue study product, be placed on immediate suppressive ART, and will be followed at quarterly intervals for 52 weeks after their last injection prior to diagnosis of HIV in order to test for safety parameters, as well as CD4 cell count and HIV viral load. After 52 weeks, they will be terminated from the study and transitioned to continued HIV-related care. **Additionally, participants in Step 2 who prematurely stop receiving injections for any reason other than HIV infection will remain blinded to their study assignment and transition to Step 3, complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual visits until all participants complete Step 2 of the study.**

Step 3:

Both arms: **Open-label daily oral TDF/FTC starting** no later than 8 weeks after the last injection (in order to cover the pharmacokinetic (PK) tail for Arm A participants), **and continued** for up to 48 weeks. Participants will then transition to locally-available HIV prevention services, including services for PrEP, if available (**and annual visits if applicable as outlined above**).

A participant with confirmed HIV infection during Step 3 will be **placed on ART and** followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of the 083HIV@hptn.org group.

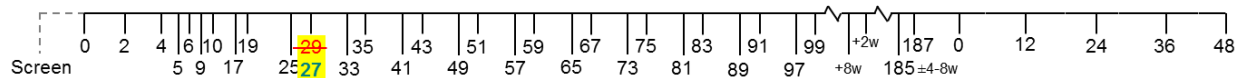
REVISION #5c, V2.0, 25 Jul 2018:

- Note: the last two bullets under Tertiary Objectives are impacted and included below.
 - To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, **and South Africa** ~~and India~~
 - To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, **and South Africa** ~~and India~~

Overview of Study Design and Randomization Scheme

LoA #1, 24 May 2016:

- Note: Only the relevant portion of the corrected scheme is depicted.



Section 1.0 – Introduction

Section 1.2.1 – Non-human Primate Studies relevant to rectal exposures

REVISION #6, V2.0, 25 Jul 2018:

- CAB LA has demonstrated activity in preventing SHIV infection in non-human primate models⁴⁵. In a preclinical study evaluating the potential of CAB LA for PrEP, 2 weekly doses of CAB LA (50 mg/kg intramuscularly [IM]) were highly protective against weekly rectal challenges with SHIV162p3 (50 tissue culture infective dose [TCID]₅₀) for up to eight exposures. In these protected animals, the plasma concentrations of CAB LA throughout the period of virus challenges were comparable to clinically-relevant concentrations in humans. In follow-up studies, a single dose of CAB LA 50 mg/kg IM one week prior to the serial weekly viral challenges with SHIV162p3 (50 TCID₅₀) were evaluated. The percent of challenges resulting in infection was calculated relative to the plasma cabotegravir protein-adjusted inhibitory concentration (PA-IC₉₀) value. None of 59 challenges resulted in infection when plasma levels were greater than 3 times the PA-IC₉₀, compared with 1 out of 22 challenges resulting in infection when plasma levels were between 1 to 3 times the PA-IC₉₀, and 11 out of 43 challenges resulting in infection when plasma levels were less than 1 times the PA-IC₉₀. Twelve out of 26 challenges resulted in infection in control animals; rectal tissue levels of cabotegravir were approximately 20% of plasma levels.⁴⁵ **Additionally, a penile SHIV infection model in rhesus macaques demonstrated 93% of protective efficacy of CAB LA against penile exposures to SHIV.⁸⁶**

Section 1.3.2 – CAB LA

LoA #3, 10 Nov 2016:

- Note: The first two paragraphs of this section are impacted and included below.

Following a single IM or subcutaneous (SC) injection of CAB LA, plasma drug concentrations increased rapidly over the first week, followed by a general trend to plateau for the remainder of the 12-week follow-up period. ~~The drug was detected in plasma up to 52 weeks, and the mean absorption limited apparent terminal phase half-life ranged from 21 to 50 days, reflecting absorption from depot site rather than elimination from the systemic circulation.~~ **Data from the ÉCLAIR study (which administered three serial injections of 800 mg CAB LA IM every 12 weeks [as 2 x 400 mg IM at each injection]) have shown that in some individuals (14 out of 83, 17%), CAB was detectable in plasma at 52 weeks post last injection⁸⁰. The CAB concentrations in these study participants ranged from 29-105 ng/ml; these values fall between the lower limit of quantitation (LOQ) of 25 ng/ml and 1 x PA-IC₉₀ (166 ng/ml).**

Additional data through 76 weeks post last injection (an additional 24 weeks longer than the current follow-up of 52-weeks post last injection) in HPTN 077 (which administers CAB LA 800 mg IM every 12 weeks in Cohort 1 and CAB LA 600 mg IM every 8 weeks after two initial injections four weeks apart in Cohort 2) will be available in approximately the fourth quarter of 2017 (for Cohort 1) and the third quarter of 2018 (for Cohort 2). These data will provide additional insight into how long cabotegravir levels may be detected after terminal injection, and help to inform the optimal duration of Step 3 of HPTN 083.

REVISION #7, V2.0, 25 Jul 2018:

- Note: the last paragraph of this section is impacted and included below.

Relevant PK parameters following CAB LA in healthy and HIV infected subjects and following simulations based on the initial and updated population PK models are listed in Table 1. **Additionally, pharmacokinetic analyses from HPTN 077, evaluating the 600mg IM dose of CAB LA at 8-week intervals after an initial 4 week interval between the first two injections, also support the choice of that dose for the Phase 3 studies of CAB LA for HIV prevention.⁸⁷**

Section 1.4 – Clinical Experience to Date: Oral CAB and CAB LA

LoA #1, 24 May 2016:

- Note: Only the relevant portion of the section is depicted, which is the fourth paragraph from the beginning of Section 1.4.

Injection site reactions (ISR) occurred in the majority of participants following IM (76% with any ISR) dosing, however, the reactions were mild and moderate (overall ISR Grade 2: 14% in IM without any Grade 3 or 4 ISRs).⁴⁹ ISRs related to CAB LA injection were common but generally mild (IM: 86%, SC: 99%) with no Grade 3 ISR AEs in Phase 1 studies. The most frequent ISRs for IM dosing were pain (71%), erythema (9%) and

nodules (7%) ~~in 2013~~). Median IM ISR durations were approximately 5 days for pain and erythema, and approximately 22 days for nodules.⁴⁹

REVISION #8, V2.0, 25 Jul 2018:

- Note: Only the relevant portion of the section is depicted, starting at the ninth paragraph from the beginning of Section 1.4.

Safety results through week ~~96-144~~ support continuation of all three oral CAB dosing arms. There have been no deaths, oral CAB-related SAEs or clinically significant AE trends identified to date in LAI116482. The most common clinical drug related AEs to date have been headache (15%), nausea (17%) and diarrhea (10%) with few oral CAB AEs leading to withdrawal from the study (744 - 4% vs EFV - 15%). Two HIV-infected participants receiving oral CAB 60 mg + ABC/3TC with pre-existing steatohepatitis developed an ALT >10x upper limit of normal (ULN) 4 weeks and 8 weeks after study initiation. Both participants remained asymptomatic with normal bilirubin levels and hepatic function, and ALT levels normalized after drug discontinuation. No other participants have required dose adjustment or discontinuation due to a change in transaminases through week 96. One participant receiving oral CAB and rilpivirine 25 mg developed ALT values >10x ULN at Week 96 likely due to acute Hepatitis C infection.

Plasma exposures after administration of CAB LA are expected to remain between the oral CAB 10 mg and 30 mg exposures. At this stage of development, a lead-in of oral CAB is being employed to determine safety and tolerability in individual participants, prior to the transition to CAB LA. The accumulated efficacy and safety data with oral CAB and CABLA in HIV-infected and HIV-uninfected participants supports continued clinical development for HIV treatment and PrEP.

A second Phase 2b study in HIV-infected, antiretroviral naïve adults ~~is currently underway~~ (LATTE-2) **is ongoing**, with 310 participants enrolled to receive oral CAB 30mg + ABC/3TC for 20 weeks followed by a long acting regimen containing CAB LA + TMC278LA or continuation of oral medications. Data from this study is limited and preliminary. One participant with Hepatitis C infection and underlying stage 3/4 liver fibrosis received oral CAB 30mg + ABC/3TC and developed possible drug induced liver injury and a second subject on oral CAB 30 mg + ABC/3TC, with steatohepatitis, developed possible drug induced liver injury approximately 6 months after initiating oral CAB. Two deaths have occurred on study, one due to a motor vehicle accident (unrelated to study products), and as noted above, one due to anoxic brain injury from status epilepticus in the setting of recreational drug use; contribution from oral CAB could not be ruled out.

Cumulative exposures of GSK1265744, through ~~01 July 2015~~ **December 2017**, are shown in Table 2.

Table 2: Cumulative Cabotegravir Exposure Estimates from Phase 1 through Phase 2b Clinical Studies

REVISION #9, V2.0, 25 Jul 2018:

- Note: the new table is included below and all footnotes from previous versions are deleted

Table 2: Cumulative Cabotegravir Exposure Estimates from Phase 1 through Phase 2b Clinical Studies Up To ~~01 July 2015~~ **December 2017**

Treatment Population/ Dose	Duration	Completed	Ongoing/ Concluded	Total
Healthy Volunteers/HIV Uninfected				
5 to 150 mg oral	Single dose	223	0	223
10 to 30 mg QD po	10 to 28 days	263	647	910
150 mg q12hr po	3 doses	40	0	40
100 – 800 mg IM/SC LA	Max 456 days	230	504	734
Any dose		584	647	1231
HIV Infected Patients				
5 to 30 mg QD po (Ph 2a)	10 days	15	0	15
10 to 60 mg QD po (Ph 2b)	Max 1946 days	0	181	181
30 mg QD po (Ph 2b/3/other)	Max 1313 days	0	944	944
Up to 800 mg IM LA	Max 1176 days	0	880	880
Any dose		15	1130	1145
ALL Participants				
Single dose oral (5 to 150 mg)		223	0	223
Repeat dose QD po (5-60 mg)		278	1772	2050
150 mg oral every 12 hours x 3		40	0	40
Single or repeat dose LA injection (100 to 800 mg)		230	1384	1614
Any dose		599	1777	2376

Section 1.4.1 – Evidence for Clinically Significant Anti-viral Activity in HIV-infected Individuals

REVISION #10, V2.0, 25 Jul 2018:

- ~~Two~~**As described above, two** Phase 2b clinical trials are ~~in progress~~**ongoing** (GSK protocol LAI116482 [LATTE] and 200056 [LATTE-2]). In the LATTE study, 181 participants were randomized to receive oral CAB (10, 30, or 60 mg once-daily, blinded doses) in combination with either TDF/FTC or abacavir-lamivudine (ABC/3TC).⁴⁸ An additional 62 participants were randomized to a control arm of open-label efavirenz (EFV) 600 mg once daily in combination with one of the two NRTIs. A week 24 interim analysis demonstrated good initial efficacy and safety of oral CAB in combination with NRTIs. The overall response rate across the three dosing arms of oral CAB were 87% <50 c/mL (FDA snapshot analysis) with minimal differences between oral CAB doses; the control arm response rate was 74% <50 c/mL. In the “maintenance” phase, participants randomized to any of the oral CAB doses who had viral loads <50 c/mL prior to week 24 were transitioned to a regimen maintaining their oral CAB dosing but substituting oral rilpivirine (RPV) 25 mg daily for the NRTI. EFV-treated participants were kept on their “induction” regimen of dual NRTIs with EFV. 96-week data (representing 72 weeks of maintenance dosing) showed virologic suppression (<50 c/mL) rates via snapshot analysis to be 79%, 85% and 93% for oral CAB administered at 10 mg, 30 mg, and 60 mg daily, and 83% for the EFV control participants. One participant randomized to oral CAB 10 mg who successfully transitioned to RPV plus oral CAB 10 mg daily experienced virologic failure at week 48 in the context of sub therapeutic (<50% expected) CAB and RPV plasma levels (partially confounded by an extreme calorie-restricted diet during weeks 40-48), and developed treatment-emergent high level integrase (Q148R) and non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance with the E138Q mutation.⁴⁸ Two additional participants experienced virologic failure on CAB-containing therapy with evidence of NNRTI-resistance only (K101K/E and E183E/K at weeks 48 and 72, respectively).⁵⁰ **Two phase 3 trials of CAB LA + RPV LA administered at 4-week intervals for maintenance of virologic suppression in HIV-infected individuals are fully enrolled and ongoing (ATLAS, FLAIR), and an additional phase 3b trial of CAB LA + RPV LA administered at 8-week intervals for maintenance of virologic suppression in HIV infected individuals is also ongoing (ATLAS-2M).**

Section 1.5 – Hepatic and Central Nervous System Adverse Events

LoA #2, 26 Jul 2016:

- Note: Only the first paragraph of this section is impacted by this change and is depicted below.

As part of the early phase development of cabotegravir (**Phase 2a HPTN 077**, Phase 2b LATTE and LATTE-2), some participants ~~with HIV infection and pre-existing liver disease~~ developed transaminase elevations, which were clinically asymptomatic and resolved rapidly with cessation of study product.

Section 1.8 – Rationale for Bone Mineral Density Subset

LoA #4, 14 Dec 2017:

- Note: Only the second paragraph (out of two) of this section is impacted and is included below.

At sites that have the ability to perform DXA scans, 175 participants in each arm (350 participants in total) will be offered participation in a DXA ~~subset study~~. DXA evaluations will be conducted for ~~subset study~~ participants at Enrollment and Weeks 57 and 105. An additional informed consent will be required for ~~subset sub-study~~ participation, ~~and participation will be stratified across regions to provide broad geographic and racial/ethnic representation in the sub-study~~. **The subset will be competitively enrolled until 350 baseline DXA scans are obtained.**

Section 1.11 – Adherence Counseling and Monitoring

LoA #1, 24 May 2016:

- Note: Only the relevant portion of the section is depicted, which is the 1st paragraph down from the beginning of Section 1.11.

It is clear that the effectiveness of daily oral TDF/FTC is tightly correlated with adherence. Therefore, a critical component of the comparison between daily oral TDF/FTC and CAB LA will be participants' ability/willingness to take a daily pill compared to a clinic-administered injection ~~on a quarterly schedule~~ **at two time points 4 weeks apart followed by every 8 weeks thereafter**. To evaluate the clinical applicability of this difference, the study will provide adherence support at baseline and at all follow-up visits for all participants in a manualized/standardized fashion commensurate with an intervention that could be easily implemented in diverse clinical settings. Any participant who has self-reported or actual returned pill-count evidence of challenges with adherence to AT MINIMUM the level of 4 doses weekly will be provided an individualized adherence intervention designed to problem-solve individual barriers to adherence.

Section 1.12 – Rationale for use of oral lead-in prior to injectable dosing

LoA #3, 10 Nov 2016:

- The CAB LA formulation has a pharmacokinetic decay rate that exposes the injected individual to detectable levels of cabotegravir for up to ~~52 weeks~~ **a year or more** after an injection (**see Section 1.3.2**). In order to maximally identify any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection, a 5-week lead-in period of daily oral (short acting) cabotegravir will be employed. This lead-in period will be evaluated with serial safety assessments prior to injectable administration. The current plans for product labeling should FDA approval be granted include an oral lead-in strategy when adequate safety is established after 4 weeks of oral drug exposure. The 5-

week exposure in this study is designed to provide uninterrupted study product coverage while awaiting return of the Week 4 safety laboratory assessments.

Section 1.14 – Rationale For Web-Based Sexual Health Promotion Score During Screening

LoA #1, 24 May 2016:

- **SexPro is a web-based tool that provides participants with a sexual health promotion score. The SexPro score was developed to estimate short-term HIV acquisition risk using data from several large cohorts of MSM in the United States and South America.⁸⁰⁻⁸⁴ Different models were developed for North and South America, based on data from these two populations. In particular, these models reflect differences in demographic and substance use effects on HIV acquisition, and required tradeoffs between goodness of fit and delivering interpretable risk information. From this, two separate SexPro interfaces were created: one for North American MSM (available in English and Spanish), and one for South American MSM (in Spanish and Portuguese). Participants answer a brief questionnaire including age, race/ethnicity (US only), behavioral risk factors, substance use, and history of sexually transmitted diseases (gonorrhea, chlamydia, and syphilis) which are used to calculate their personalized HIV risk score reflecting their likelihood of HIV acquisition at six months. Scores range from 1 (highest risk) to 20 (lowest risk) based upon a positive sexual health promotion framing. The SexPro score for the North American model has been subsequently validated in two contemporary longitudinal cohorts of MSM – HPTN 061 and HVTN 505 – and shows good model fit, especially among Black MSM in HPTN 061. A SexPro score of 16 or lower showed good sensitivity (75.4%) and specificity (51.8%) in HVTN 505. All HIV seroconversions in HPTN 061 occurred below this value; this cut-off was chosen to identify MSM at high risk for HIV infection, and to maximize sensitivity of the tool for Black MSM in the US. The SexPro score, using a score cut-off of 16 or lower, will be used in addition to the current behavioral risk inclusion criteria for the US-based cohort; participants who do not qualify on the basis of the current behavioral risk will be eligible with a risk score of 16 or lower. This recognizes that young men of color in the US are at risk of acquiring HIV with less self-reported risk than older white men. SexPro will also be administered to MSM outside of US, but will not be used as part of the inclusion criteria, as this has not yet been validated in separate cohorts.**

Section 2.0 – Study Objectives and Design

Section 2.3 – Tertiary Objectives

REVISION #11, V2.0, 25 Jul 2018:

- Note: Only the fourth and fifth bullets are impacted and included below.
 - To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, **and** South Africa ~~and India~~
 - To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, **and** South Africa ~~and India~~

Section 2.5 – Study Design and Overview

REVISION #12, V2.0, 25 Jul 2018:

- Note: Step 1 and Step 2 are impacted and depicted below.

Step 1:

- Arm A - Daily oral CAB (30 mg tablets) and daily oral placebo for TDF/FTC for 5 weeks.
- Arm B - Daily oral TDF/FTC and daily oral placebo for CAB for 5 weeks.

Any participant that becomes HIV-infected during Step 1 of the study will permanently discontinue study product and will be terminated from the study, and referred for HIV-related care. **Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will remain blinded to their study assignment and be asked to attend annual visits until all participants complete Step 2 of the study.**

Step 2:

- Arm A – Injections of CAB LA at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5, and daily oral placebo for TDF/FTC. Injections will consist of 600 mg of CAB LA administered as one 3 mL injection.
- Arm B: Daily oral TDF/FTC and injections of placebo for CAB LA on the same schedule as Arm A beginning at week 5. Injections will consist of the same volume (3 mL) as Arm A participants.

This step will continue until the required number of incident HIV endpoints is reached, estimated to be when the final participant reaches approximately 60 weeks on Step 2 (**study** week 65 for the final participant).

Participants **in Step 2** who ~~permanently discontinue~~**prematurely stop** receiving injections ~~before their study participation ends~~ for any reason other than HIV infection will remain blinded to their study assignment and will ~~follow~~**transition to Step 3, complete the schedule in Step 3, starting no later than 4-8 required 48 weeks after their last injection****of follow-up in Step 3, and will then be asked to attend annual visits until all participants complete Step 2 of the study.**

Any participant that becomes HIV infected during Step 2 of the study will permanently discontinue study product and will be followed at quarterly intervals for approximately 52 weeks in order to test for safety parameters, as well as CD4 cell count and HIV viral load.

LoA #4, 14 Dec 2017:

- Note: The second paragraph under Step 3 of this section is impacted and included below.

Step 3:

Participants with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the ~~CMC~~ 083HIV@hptn.org group.

Section 3.0 – Study Population

Section 3.1 – Inclusion Criteria

LoA #1, 24 May 2016:

- Note: Only the relevant portion of this section is depicted.
 - At high risk for sexually acquiring HIV infection based **on** self-report of at least one of the following:
 - Any condomless receptive anal intercourse in the 6 months prior to enrollment (condomless anal intercourse within a monogamous HIV seronegative concordant relationship does not meet this criterion)
 - More than five partners in the 6 months prior to enrollment (regardless of condom use and HIV serostatus, as reported by the enrollee)
 - Any stimulant drug use in the 6 months prior to enrollment
 - Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months prior to enrollment
 - **SexPro score of ≤ 16 (US sites only)**

CM #2, 19 Oct 2017:

- Note: Only one sub bullet is impacted by the clarification in this section, and only the corresponding main bullet to which the sub bullet is under is included below.
 - In general good health, as evidenced by the following laboratory values, which must be from specimens obtained within 45 days prior to study enrollment:

- Non-reactive / negative HIV test results*
- Hemoglobin > 11 g/dL,
- Absolute neutrophil count > 750 cells/mm³
- Platelet count ≥ 100,000/mm³
- Calculated creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault equation
- Alanine aminotransferase (ALT) < 2 times the upper limit of normal (ULN)
- Total bilirubin ≤ 2.5 times ULN
- Hepatitis B virus (HBV) surface antigen (HBsAg) negative
- HCV Ab negative
- No Grade 3 or higher laboratory abnormalities

~~*HIV-uninfected, based on HIV test results obtained at Screening and just prior to randomization at the Enrollment visit. All HIV test results from the Screening visit must be obtained and must all be negative/non-reactive. This includes testing for acute HIV infection, which must be performed within 14 days of Enrollment. In addition, at least one HIV test result obtained at the Enrollment visit must be obtained prior to randomization in to the study~~ **provision of study product** and must be negative/non-reactive. Individuals who have one or more reactive or positive HIV test results will not be enrolled, even if subsequent confirmatory testing indicates that they are not HIV-infected (see SSP Manual).

REVISION #13, V2.0, 25 Jul 2018:

- Note: Only one sub bullet is impacted by the clarification in this section, and only the corresponding main bullet to which the sub bullet is under is included below.
 - In general good health, as evidenced by the following laboratory values, which must be from specimens obtained within 45 days prior to study enrollment:
 - Non-reactive / negative HIV test results*
 - Hemoglobin > 11 g/dL,
 - Absolute neutrophil count > 750 cells/mm³
 - Platelet count ≥ 100,000/mm³
 - Calculated creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault equation **(use sex at birth for calculation)**
 - **Although not protocol exclusionary, sites should carefully consider the advisability of enrolling participants with calculated creatinine clearance between 60-70 mL/min, as limited changes in creatinine clearance during study conduct**

will lead to protocol-mandated product holds and may alter the risk-benefit considerations of study participation

- Alanine aminotransferase (ALT) < 2 times the upper limit of normal (ULN)
- Total bilirubin \leq 2.5 times ULN
- Hepatitis B virus (HBV) surface antigen (HBsAg) negative
- HCV Ab negative
- No Grade 3 or higher laboratory abnormalities **on any laboratory tests obtained at screening, including tests obtained as part of a panel of tests ordered to obtain the protocol-required laboratory test results.**

Section 3.2 – Exclusion Criteria

LoA #1, 24 May 2016:

- Note: Only the relevant portion of this section is depicted.
 - Known or suspected allergy to study product components (active or placebo), **including egg or soy products (egg and soy products are contained in Intralipid)**
 - Surgically-placed **or injected silicone/industrial product** buttock implants, per self-report
 - Alcohol or substance use that, in the opinion of the study investigator, would jeopardize the safety of the participant on study (e.g., provided by self-report, or found upon medical history and examination or in available medical records).
 - History of seizure disorder, per self-report
 - **QTc interval (B or F) > 500 msec**

LoA #2, 26 Jul 2016:

- Note: Only the exclusion criterion that is impacted by this change is depicted below (and takes precedence over LoA #1).
 - Surgically-placed or injected ~~silicone/industrial product~~ buttock implants **or fillers**, per self-report. **Contact the CMC for guidance regarding questions about individual cases.**

Section 3.4 – Co-Enrollment Guidelines

REVISION #14, V2.0, 25 Jul 2018:

- In general, participants in this study will not be allowed to take part in other concurrent ~~interventional~~-research studies during their participation in the study. This is due in part to concerns about participant study burden, American Red Cross-mandated limitations on

per-unit-time phlebotomized blood volumes, to avoid potential unblinding of this or other studies, and to avoid confounding in the interpretation of the study data. The Clinical Management Committee (CMC) should be consulted for any possible exceptions, ~~including for observational studies.~~

Section 3.6 – Participant Withdrawal

Revision #15, V2.0, 25 Jul 2018:

- Note: The first paragraph of this section is impacted and included below.

Regardless of the participant retention methods described in Section 3.5, participants may voluntarily withdraw from the study for any reason at any time. ~~The Investigator also may withdraw~~ **In general, participants should not be withdrawn from the study during the blinded, randomized portion of the study except in order the case of a) withdrawal of consent; b) death; c) extreme/unusual circumstances to protect the participant safety and; or d) if they are unwilling or unable to comply with required study procedures. Any such safety-related participant terminations should only be implemented** after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others.

Section 4.0 – Study Product Considerations

Section 4.1 – Study Product Regimens/Administration/Formulation Content

LoA #4, 14 Dec 2017:

- Study Product Regimens

Step 1 - Participants will be randomized 1:1 to one of two study arms:

- Arm A: Oral CAB tablets 30 mg, **one tablet orally daily for five weeks, with or without food and AND** placebo for TDF/FTC tablet, ~~two one tablets orally~~ daily for 5 weeks, with or without food
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination tablets, **one tablet orally daily for five weeks, with or without food and AND** placebo for oral CAB tablets, **orally two tablets** daily for 5 weeks, with or without food

Step 2 – Blinded injections and blinded daily oral pills:

- Arm A: CAB LA 600 mg administered as one 3 mL (600 mg) **intramuscular (IM)** injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter, **and AND** placebo for TDF/FTC ~~daily oral~~ tablet, **one tablet orally daily with or without food**
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination ~~daily oral~~ tablets, **one tablet orally daily, with or without food and AND** placebo for CAB LA

(Intralipid 20% fat emulsion infusion) administered as one 3mL ~~(600 mg)~~
intramuscular (IM) injection in the gluteal muscle as two time points 4 weeks
apart and every 8 weeks thereafter

Step 3: ~~For a~~ All participants **transitioned to this step**, including those who permanently
discontinue receiving injections before their Step 2 participation in the study ends, **will**
receive open-label TDF/FTC 300 mg/200 mg fixed dose combination ~~daily oral~~ tablets,
one tablet **orally** daily for up to 48 weeks.

Section 4.2.1 – Oral Product

REVISION #16, V2.0, 25 Jul 2018:

- Note: The first two paragraphs are impacted and included below:

Oral CAB tablets 30 mg are formulated as white to almost white oval-shaped coated
tablets for oral administration. The tablets are packaged in high density polyethylene
(HDPE) bottles with child-resistant closure that include an induction seal. The bottles
contain a desiccant. The bottles should be stored up to ~~25~~**30** degrees Celsius (~~25°~~**30° C, 86**
° Fahrenheit) and protected from moisture.

Placebo tablets for oral CAB are formulated as white to almost white oval-shaped coated
tablets to visually match the active oral CAB tablets. The tablets are packaged in high
density polyethylene (HDPE) bottles with child-resistant closure that include an induction
seal. The bottles contain a desiccant. The bottles should be stored up to ~~25~~**30** degrees
Celsius (~~25°~~**30° C, 86° Fahrenheit**) and protected from moisture.

Section 4.2.2 – Injectable Suspension

LoA #4, 14 Dec 2017:

- Note: Only the first paragraph of this section is impacted and is included below.

CAB LA is formulated as a sterile white to slightly colored suspension containing
~~400mg/2mL~~ **200 mg/mL** of CAB LA for administration by intramuscular (IM). The
product is packaged in a ~~3-mL vials~~ **glass vial**. Each vial is for single use containing a
nominal fill of 2mL (400 mg); **or 3mL (600 mg)**, and does not require dilution prior to
administration. CAB LA injectable suspension is to be stored at 2 degrees ~~e~~Celsius to 30
degrees ~~e~~Celsius (2° C – 30° C), do not freeze.

REVISION #17, V2.0, 25 Jul 2018:

- Note: The first paragraph of this section is impacted and is included below.

CAB LA is formulated as a sterile white to slightly colored suspension containing 200
mg/mL of CAB LA for administration by intramuscular (IM). The product is packaged in
a glass vial. Each vial is for single use containing a nominal fill of 2mL (400 mg) or 3mL
(600 mg), and does not require dilution prior to administration. CAB LA injectable
suspension is to be stored ~~at 2 degrees Celsius~~**up to 30 degrees Celsius (2°–30° C)**, do
not freeze.

Section 4.6 – Other Study Product Dispensing Considerations

REVISION #18, V2.0, 25 Jul 2018:

- Note: This section is new to the protocol and includes the text below.

While it is not required, it is recommended that sites dispense two bottles of each study product (TDF/FTC or placebo and CAB or placebo) at Week 0, two bottles of oral TDF/FTC or placebo at Week 5, and three bottles at each dispensation visit throughout Step 2 to ensure an extra month supply between visits. Participants should be advised to bring open bottles to appointments, finish an open bottle before opening a new one, and should not combine or transfer pills between open bottles. A formal pill count is not required in Step 2 (or Step 3), but an open bottle can be used to assist with determining refill quantity (that is, whether there is sufficient remaining oral study product supply in the participant's possession that only two bottles need be dispensed and still maintain a three-month supply in the participant's possession).

It is important to dispense all study products at each visit at which study product dispensation is scheduled per protocol. For example, if during Step 2 a participant reports for an injection visit but refuses the injection or does not receive the injection for any other reason, oral study product should not be dispensed. Participants should either receive all study products at each visit where study product is scheduled to be dispensed, or no study products.

Section 5.0 – Study Procedures

LoA #4, 14 Dec 2017:

- Overviews of the study visit and procedures schedules are presented in Appendices I ~~a-e~~ **a - d**, and Appendix II in the event of suspected and confirmed HIV infection. **Appendices I e – g include the required HIV testing algorithm for screening, enrollment and follow-up, respectively (these are also included in the SSP).** Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites are included in the SSP Manual.

Section 5.1 – Screening

LoA #1, 24 May 2016:

- Note: Only the relevant portion of this section is depicted.

Administrative, Behavioral, and Regulatory Procedures

- Informed consent
- **Administer SexPro assessment (US only for inclusion purposes; South American sites only for data collection purposes currently)**

- Locator information
- HIV counseling
- Offer condoms and lubricant

Section 5.2 – Step 1: Week 0 – Enrollment

LoA #1, 24 May 2016:

- Note: Only the relevant portion of this section is depicted.

Clinical Procedures

- Complete medical history and complete physical exam, including concomitant medications (may be performed during screening at the discretion of the Investigator of Record or their designee)
- DXA (only if part of BMD subset, and may be performed ~~-14~~ **30** days/+ ~~14~~ **7** days of enrollment), and dietary calcium and Vitamin D assessment

REVISION #19, V2.0, 25 Jul 2018:

- Note: Only the relevant portion of this section is depicted below.

Clinical Procedures

- Complete medical history and complete physical exam, including concomitant medications (may be performed during screening at the discretion of the Investigator of Record or their designee)
- ~~DXA (only if part of BMD subset)~~ **Subset only: DXA scan, and dietary calcium and Vitamin D assessment. The scan** may be performed -30 days/+7 days of enrollment), ~~and dietary calcium and Vitamin D assessment.~~
- Blood collection (collect prior to administration of study product)
- Urine collection for urinalysis
- Urine collection for Neisseria gonorrhea (GC) and Chlamydia trachomatis (CT)
- Rectal swab for GC/CT testing
- Dispense oral study product (enough for 5 weeks) (Dosing should begin on the day of Enrollment or no later than 24 hours ~~of~~ **after** Enrollment)

Section 5.3 – Step 1: Weeks 2 and 4 – Oral Safety Visits

LoA #4, 14 Dec 2017:

- Note: Only the “Notes for Weeks 2 and 4” portion of this section is impacted and included below.

All HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed. If any of these tests is reactive/positive, study drug should be discontinued.

A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is \leq Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is $<$ Grade 2 at Week 4, the participant may proceed to Step 2 injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually for HIV testing ~~only~~ **until all participants complete Step 2 of the study**. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1.

A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually for HIV testing ~~only~~ **until the all participants complete Step 2 of the study**. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1.

Excluding ALT, any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.

Grade 3 adverse events deemed related to study product, or a Grade 3 ALT, or any Grade 4 adverse event will lead to permanent study product discontinuation, and the participant will be followed annually for HIV testing ~~only~~ **until the all participants complete conclusion of Step 2 of the study**. AEs will be followed until resolution (\leq grade 1) in consultation with the CMC.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually for HIV testing ~~only~~ **until the all participants complete conclusion of Step 2 of the study**. All such cases must be reported to the CMC.

The CMC should be contacted for guidance regarding pill counts resulting in less than 75% adherence prior to the Week 5 First Injection Visit, or any other concerns regarding adherence.

For participants who do not transition to Step 2 as outlined above, the following procedures will take place (see also Appendix ID):

- **Review/update locator information**
- **Targeted medical history and targeted physical exam, with concomitant medications update**
- **HIV pre and post-test counseling**
- **HIV testing, plasma storage, DBS storage**
- **Offer condoms and lubricant**

REVISION #20, V2.0, 25 Jul 2018:

- Note: Only the “Notes for Weeks 2 and 4” portion of this section is impacted and included below.

All HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed. If any of these tests is reactive/positive, study drug should be discontinued.

A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is \leq Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is $<$ Grade 2 at Week 4, the participant may proceed to Step 2 injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually ~~for HIV testing~~ until all participants complete Step 2 of the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1.

A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually ~~for HIV testing~~ until all participants complete Step 2 of the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1.

Excluding ALT, any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.

Grade 3 adverse events deemed related to study product, or a Grade 3 ALT, or any Grade 4 adverse event will lead to permanent study product discontinuation, and the participant will be followed annually ~~for HIV testing~~ until all participants complete Step 2 of the study. AEs will be followed until resolution (\leq grade 1) in consultation with the CMC.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for

adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually for HIV testing until all participants complete Step 2 of the study. All such cases must be reported to the CMC.

~~The CMC should be contacted for guidance regarding pill counts resulting in less than 75% adherence prior to the Week 5 First Injection Visit, or any other concerns regarding adherence.~~ **Participants with pill counts resulting in less than 50% adherence as assessed by pill count at the Week 4 visit will not be allowed to transition to Step 2. These participants will be asked to report for annual visits until all participants in the study have completed Step 2. Refer to Section 5 of the SSP for instructions regarding participants who forget to bring their pill bottles to the Week 4 visit.**

For participants who do not transition to Step 2 as outlined above, the following procedures will take place (see also Appendix ID):

- Review/update locator information
- Targeted medical history and targeted physical exam, with concomitant medications update
- HIV pre and post-test counseling
- HIV testing, plasma storage, DBS storage
- Offer condoms and lubricant

Section 5.4 – Step 2: Weeks 5 – First injection visit in Step 2

REVISION #21, V2.0, 25 Jul 2018:

- Note: Only the “Notes” portion of this section is impacted and included below.

NOTE 1: All HIV test results from previous visits and at least one HIV test result from the Week 5 visit must be available and confirmed to be negative/non-reactive PRIOR to injection of study product. The injection must not be given if any HIV test is reactive/positive.

Results from all Week 4 clinical and laboratory evaluations (e.g., chemistry, LFTs, hematology) must be available and be reviewed by the IoR or their designee prior to injection.

NOTE 2: Refer to Section 5 of the SSP regarding instructions for split visits where the injection was not administered during the first half of the split visit, and for merged visits where in unforeseen circumstances, a safety visit and an injection visit occur on the same day.

Section 5.6 – Step 2: All remaining visits where injections occur - Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185

REVISION #22a V2.0, 25 Jul 2018:

- Note: Only the relevant portion of this section is depicted below.

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications
- ECG (only at Weeks 57, 105, 153)
- ~~DXA (in BMD subset only, and (only at Weeks 57, and 105))~~: **DXA scan**, and dietary calcium and Vitamin D assessment. **These scans may be performed +/- 8 weeks of each visit).**

REVISION #22b, V2.0, 25 Jul 2018:

- Note: Only the “Notes” portion of this section is impacted and included below.

NOTE 1: All HIV test results from previous visits and at least one HIV test result from the current injection visit must be available and confirmed to be negative/non-reactive PRIOR to injection of study product. The injection must not be given if any HIV test is reactive/positive.

Results from the other laboratory evaluations (e.g., chemistry, LFTs, hematology) from the visit prior to the injection visit must be available and be reviewed by the IoR or designee prior to injection.

NOTE 2: Refer to Section 5 of the SSP regarding instructions for split visits where the injection was not administered during the first half of the split visit, and for merged visits where in unforeseen circumstances, a safety visit and an injection visit occur on the same day.

Section 5.9 – ~~Injection~~ Visit Windows

LoA #4, 14 Dec 2017:

- The visit windows for all visits, including injection visits, are outlined in the SSP Manual. In brief, the **target** visit window for injection visits for the Week 5 and 9 injections is +/- 3 days, and is +/- 7 days for all other injections visits. ~~If a participant is unable to report to the visit during this time frame, or if the participant misses their appointment within this time frame, the CMC must be contacted for consultation regarding whether rescheduling outside of the visit window is allowable.~~ **Broader, allowable visit windows are also defined in the SSP Manual and are contiguous. Each study visit, including the injection visit, should ideally be conducted within the target date range. When that is not possible, visits outside of the target dates and inside the allowable windows may be completed; however, for injection visits, the CMC must be consulted in advance regarding additional clinical considerations for the timing of injections.**

REVISION #23, V2.0, 25 Jul 2018:

- The visit windows for all visits, including injection visits, are outlined in the SSP Manual. In brief, the target visit window for injection visits for the Week 5 and 9 injections is +/- 3 days, and is +/- 7 days for all other injections visits. Broader, allowable visit windows are also defined in the SSP Manual and are contiguous. Each study visit, including the injection visit, should ideally be conducted within the target date range. When that is not possible, visits outside of the target dates and inside the allowable windows may be completed; ~~however, for~~. **Additionally, and as already outlined above, the windows for the DXA subset are -30/+ 7 days for Enrollment, and +/- 8 weeks for Weeks 57 and 105.**

It is not required to contact the CMC for out of target visit window injection visits; ~~the CMC must be consulted~~ provided that they are a minimum of 6 weeks from the last injection and a maximum of 15 weeks from the prior injection. It is required to contact the CMC for guidance in advance regarding additional clinical considerations for the timing of injections. ~~cases outside of these parameters.~~

Section 5.11 – Procedures for Participants Who Do Not Complete the Full Course of Injections

LoA #3, 10 Nov 2016:

- Participants on either arm who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open-label TDF/FTC according to Step 3 Arm A assessments; such participants will remain blinded to their original randomized assignment.

Participants **in Step 1 of the study** who are unable to **transition to Step 2 of the study** ~~receive the first injection~~ for any reason **other than HIV infection** will be ~~terminated from the study~~ **followed on an annual basis until the conclusion of Step 2 of the study (refer to SSP Manual). Participants with confirmed HIV infection during Step 1 of the study** ~~If the reason is due to HIV infection, those participants will not transition to Step 2 of the study, but will~~ be referred to care and will be terminated from the study.

Participants in Step 2 of the study that no longer receive injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study. Participants in Step 2 of the study with confirmed HIV infection will be followed according to Appendix II.

Sites should contact 083HIV@hptn.org for guidance regarding study visit procedures for participants that become HIV-infected during Step 3 of the study.

LoA #4, 14 Dec 2017:

- ~~Participants on either arm who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open-label TDF/FTC according to Step 3 Arm A assessments; such participants will remain blinded to their original randomized assignment.~~

Participants in Step 1 of the study who are unable to transition to Step 2 of the study for any reason other than HIV infection will be **asked to attend annual follow-up visits for**

HIV testing until all participants complete Step 2 of the study. (refer to SSP Manual). These participants will remain blinded to their original randomized assignment until all participants Step 2 of the study. Participants with confirmed HIV infection during Step 1 of the study will not transition to Step 2 of the study, but will be referred to care and will be terminated from the study.

Participants in Step 2 of the study that **prematurely no longer receive stop receiving** injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study. **Once that participant has completed the required 48 weeks on Step 3, they will then be transitioned to local prevention services and asked to continue to attend annual follow-up visits for HIV testing until all participants complete Step 2 of the study, if it is still ongoing at the time of their individual completion of the 48 weeks of open label TDF/FTC provision.** These participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study. Participants in Step 2 of the study with confirmed HIV infection will be followed according to Appendix II.

Sites should contact 083HIV@hptn.org for guidance regarding study visit procedures for participants that become HIV-infected during Step 3 of the study.

~~Participants who are unable to receive the first injection for any reason will be terminated from the study. If the reason is due to HIV infection, those participants will be referred for care and will be terminated from the study.~~

For participants that transition to annual HIV testing as outlined above, the following procedures will take place (see also Appendix ID):

- **Review/update locator information**
- **Targeted medical history and targeted physical exam, with concomitant medications update**
- **HIV pre and post-test counseling**
- **HIV testing, plasma storage, DBS storage**
- **Offer condoms and lubricant**

REVISION #24, V2.0, 25 Jul 2018:

- Participants in Step 1 of the study who are unable to transition to Step 2 of the study for any reason other than HIV infection will be asked to attend annual ~~follow-up~~ visits ~~for HIV testing~~ until all participants complete Step 2 of the study. These participants will remain blinded to their original randomized assignment until all participants **complete** Step 2 of the study. Participants with confirmed HIV infection during Step 1 of the study will not transition to Step 2 of the study, but will be referred for care and will be terminated from the study.

Participants in Step 2 of the study that prematurely stop receiving injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study. Once that participant has completed the required 48 weeks on Step 3, they will then be transitioned to local prevention services and asked to continue to attend annual ~~follow-up~~ visits ~~for HIV testing~~ until all participants complete Step 2 of the study, if it is still ongoing at the time of their individual completion of the 48 weeks of open label

TDF/FTC provision. These participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study. Participants in Step 2 of the study with confirmed HIV infection will be followed according to Appendix II.

Sites should contact **083HIV@hptn.org** for guidance regarding study visit procedures for participants that become HIV-infected during Step 3 of the study.

For participants that transition to annual ~~HIV testing~~ visits as outlined above, the following procedures will take place (see also Appendix ID):

- Review/update locator information
- Targeted medical history and targeted physical exam, with concomitant medications update
- HIV pre and post-test counseling
- HIV testing, plasma storage, DBS storage
- Offer condoms and lubricant

Section 5.12.1 – Emergency Unblinding for Medical Reasons

REVISION #25, V2.0, 25 Jul 2018:

- Note: This section is new to the protocol and includes the text below.

If, in the judgment of the site investigator of record (IoR), or in the judgment of the participant's medical provider and the site IoR, a medical event is of sufficient extreme severity that it requires the immediate unblinding of a participant, the site IoR may proceed with unblinding a participant per the instructions in Appendix VI of the SSP (Unblinding Medical Emergency) and any separate applicable instructions provided by the HPTN SDMC. Emergency unblinding is expected to be extremely rare. It should only occur in the setting of a potentially life threatening clinical event, and if knowing the participant's treatment assignment would affect decisions regarding the participant's immediate medical management. Both conditions must be satisfied.

Section 5.13.1 – Screening and Enrollment

LoA #4, 14 Dec 2017:

- Individuals who have one or more reactive or positive HIV tests at **the** Screening or Enrollment **visit** are not eligible to participate in this study. Furthermore, at the Screening and Enrollment **visit** (at Enrollment, prior to randomization; **and for sites that do split enrollment visits due to physical location constraints, prior to administration of study product**), individuals with any signs or symptoms consistent with acute (pre-seroconversion) HIV infection will not be enrolled, unless acute HIV infection is ruled out with appropriate laboratory testing, in consultation with the CMC. Signs and symptoms consistent with acute HIV infection will be included in the SSP Manual.

Section 5.13.2 – Follow-up (after study Enrollment)

LoA #4, 14 Dec 2017:

- Note: Only the sixth paragraph of this section is impacted and included below.

Participants with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the ~~CMC~~ 083HIV@hptn.org group.

Section 5.14 – Sexually Transmitted Infections

REVISION #26, V2.0, 25 Jul 2018:

- Testing for GC/CT and syphilis will occur throughout the study. Testing will be performed at the local laboratory. For rectal swabs, if testing cannot be performed at the local laboratory, testing at another laboratory may be arranged (see SSP Manual).

Participants will be referred for treatment of STIs as per local guidelines. Symptomatic screening for STIs beyond what is required by the protocol will be **performed** at a site's discretion and ~~costs~~ **costs associated may come out of each site's respective per participant study reimbursements.**

~~Positive testing~~ **Any positive/reactive laboratory test results for syphilis should from the time of study enrollment and any positive/reactive test during the study must be** referred to the CMC for adjudication accompanied by any prior testing and treatment results. **The communication with the CMC should occur prior to the subsequent study visit at which the positive/reactive testing is resulted. Cases of syphilis discovered prior to study participation should be documented as a pre-existing condition.**

Sites will report STIs into the study database on the Adverse Event e-CRF as well as the STI e-CRF. Further instructions regarding reporting STIs into the database are included in Section 9 of the SSP.

Section 5.15 – Hepatitis B and Hepatitis C

REVISION #27, V2.0, 25 Jul 2018:

- Note: Only the first paragraph of this section is impacted and included below.

Testing for HBV and HCV will be performed at Screening (HBsAg and HCAb⁺). Persons ~~positive for these~~ **whose screening tests results are not negative** will ~~not be allowed to enroll in the~~ **excluded from study participation** and will be referred to their primary provider for management. Persons with a positive HCV antibody test at Screening will be excluded from the study, even if confirmatory HCV RNA is undetectable. At Enrollment, participants will be tested for HBV surface antibody (HBsAb), and HBV Core antibody (HBcAb). Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be referred for HBV vaccination. For participants who do not have evidence of HBV immunity at Enrollment, HBV testing should be repeated at the discretion of the

IoR or designee during the study if clinically indicated, if the participant has elevated AST/ALT results (elevated level at discretion of IoR or designee), or if the participant expresses a concern about having acquired HBV infection after enrollment. Refer to the SSP Manual for persons who have a positive result for HBcAb only.

Section 5.17 – Criteria for Early Termination of Study Participation

REVISION #28, V2.0, 25 Jul 2018:

~~Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the CMC, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP and US FDA), or site IRBs terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records.~~

Refer to Section 3.6 of the protocol.

Section 6.0 – Safety Monitoring and Adverse Event (AE) Reporting

Section 6.3 – Adverse Event Definition and Reporting

LoA #4, 14 Dec 2017:

- Note: Only the third paragraph of this section is impacted and included below.
Study site staff will document in source documents and the appropriate e-CRF AEs (Grade 2 and higher **clinical AEs, as well as Grade 2 and higher laboratory AEs**, and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on **AE e-CRFs**) reported by or observed in enrolled (**defined as after randomization has occurred**) study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, ~~November 2014~~ **2.1 corrected, July 2017**. ~~This version will be used for the entire duration of the study.~~

REVISION #29, V2.0, 25 Jul 2018:

- Note: Only the third paragraph of this section is impacted and included below.
Study site staff will document in source documents and the appropriate e-CRF AEs (Grade 1 and higher clinical AEs, as well as Grade 2 and higher laboratory AEs, and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on **AE e-CRFs**) reported by or observed in enrolled (defined as after randomization has occurred) study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, July 2017. **STIs will be dually reported on the AE e-CRF as well as the STI e-CRF (see Section 9 of the SSP for further details related to STI reporting into the study database).**

Section 6.4 – Expedited Adverse Event Reporting

REVISION #30, V2.0, 25 Jul 2018:

- Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/safetyandpharmacovigilance>. <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>.

Section 6.4.1 – Reporting to DAIDS

REVISION #31, V2.0, 25 Jul 2018:

The DAIDS Adverse Event Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. **This form is available on the DAIDS RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting>.** For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

~~Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.~~

For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.

Section 6.4.2 – Reporting Requirements for this Study

REVISION # 32, V2.0, 25 Jul 2018:

- Note: The first three paragraphs of this section are impacted and included below.

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE manual, will be used for this study (the definition of an SAE is also included in the manual).

In addition to SAEs, sites will report in an expedited manner the following results ~~(must be both in order to require expedited reporting):~~

- ALT \geq 3xULN AND total bilirubin \geq 2xULN **(must be both in order to require expedited reporting)**
- Any seizure event

These reporting requirements are required for each study participant from enrollment (~~week 0~~) until their follow-up in the study ends. After this time, sites must report **to DAIDS** serious, unexpected, clinical suspected adverse drug reactions, **as defined in Version 2.0 of the DAIDS EAE manual**, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

LoA #4, 14 Dec 2017:

- Note: Only the last paragraph in this section is impacted and included below.
Information on Grade ~~2~~ **1** and higher AEs will be included in reports to the US FDA, and other government and regulatory authorities as applicable. Site staff will report information regarding AEs to their IRB in accordance with all applicable regulations and local IRB requirements.

Section 6.4.3 – Grading Severity of Events

LoA #4, 14 Dec 2017:

- The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, **Corrected** Version ~~2.0, November 2014~~ **2.1, July 2017**, will be used for ~~the entire duration of the study for~~ determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

REVISION #33, V2.0, 25 Jul 2018:

- The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. ~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.~~

Section 7.0 – Statistical Considerations

Section 7.5.3 – Tertiary Endpoints

LoA #1, 24 May 2016:

- Note: Only the relevant portion of this section is depicted.
Adherence to study product during step 2: For CAB-LA/Placebo CAB-LA scheduled injections received; for TDF/FTC/Placebo TDF/FTC pill dispensing, ~~pill counts~~

Section 7.11.4 – Analyses of Tertiary Objectives

REVISION #34, V2.0, 25 Jul 2018:

- Note: Two bullet points are impacted and included below.
 - To compare the resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, **and** South Africa ~~and India~~
 - To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, **and** South Africa ~~and India~~

Section 8.0 – Human Subjects Considerations

Section 8.4 – Confidentiality

LoA #4, 14 Dec 2017:

- Note: Only the second paragraph in this section is impacted and depicted below.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; pharmaceutical sponsors; representatives of the HPTN LOC, SDMC, and/or LC; the US FDA, OHRP, ~~other government and regulatory authorities~~, **other U.S., local and international regulatory entities**, and/or site IRBs.

Section 10.0 – Administrative Procedures

Section 10.3 – Study Coordination

REVISION #35, V2.0, 25 Jul 2018:

- Note: Only the third paragraph in this section is impacted and included below.

Electronic sStudy case report forms will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, entered, and cleaned using the **MediData Rave electronic HPTN SDMC DataFax** ~~DataFax~~ data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Section 10.4 – Study Monitoring

REVISION #36, V2.0, 25 Jul 2018:

- Note: Only the last paragraph is impacted and included below.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, ViiV Healthcare, Gilead Sciences, Inc., site IRBs/ECs, and **other US, local, and international** regulatory authorities (~~OHRP and US FDA~~). A site visit log will be maintained at each study site to document all visits.

Section 11.0 – References

LoA #1, 24 May 2016:

- References #80 – 84 were added:

80. Koblin BA, Chesney MA, Husnik MJ, et al. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. Am J Public Health 2003;93:926-32.

81. Koblin BA, Mayer KH, Noonan E, et al. Sexual risk behaviors, circumcision status and pre-existing immunity to adenovirus type 5 among men who have sex with men participating in a randomized HIV-1 vaccine efficacy trial: Step Study. J Acquir Immune Defic Syndr 2012.

82. Bartholow BN, Goli V, Ackers M, et al. Demographic and behavioral contextual risk groups among men who have sex with men participating in a phase 3 HIV vaccine efficacy trial: implications for HIV prevention and behavioral/biomedical intervention trials. J Acquir Immune Defic Syndr 2006;43:594-602.

83. Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual Risk, Nitrite Inhalant Use, and Lack of Circumcision Associated With HIV Seroconversion in Men Who Have Sex With Men in the United States. J Acquir Immune Defic Syndr 2005;39:82-9.

84. Sanchez J, Lama JR, Peinado J, et al. High HIV and ulcerative sexually transmitted infection incidence estimates among men who have sex with men in Peru: awaiting for an effective preventive intervention. J Acquir Immune Defic Syndr 2009;51 Suppl 1:S47-51.

LoA #3, 10 Nov 2016:

- Reference #85 was added:

85. ECLAIR Study of Cabotegravir LA Injections: Characterization of Safety and PK During the “PK Tail” Phase. Ford S; Stancil B; Markowitz M, et al. HIV

Research for Prevention, Chicago, IL, USA, October 17-21, 2016. Abstract OA12.06LB.

REVISION #37, V2.0, 25 Jul 2018:

- References #86 and #87 are added:

86. Dobard, C et al. Long-Acting Cabotegravir Protects Macaques Against Repeated Penile SHIV Exposures. Abstract #83. Conference on Retroviruses and Opportunistic Infections 2018; Boston, MA.

87. Landovitz R, et al. Safety, Tolerability, and Pharmacokinetics of Long-Acting Injectable Cabotegravir in Low-Risk HIV-uninfected Women and Men and Women, HPTN 077. Abstract #TUAC0106LB. 9th IAS Conference on HIV Science, 23-26 July 2017, Paris, France.

Appendix I-IV – Schedule of Procedures and Evaluations

Appendix IA – Schedule of Procedures and Evaluations – Screening; Step 1 – Blinded Daily Oral Pills

LoA #1, 24 May 2016:

- Note: Only the relevant section of the screening Schedule of Procedures and Evaluations is depicted.

	Screening	Step 1		
		DAY 0/ Enrollment	WEEK 2	WEEK 4
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Informed consent	X			
SexPro assessment (US sites only for inclusion; South American sites only for data collection)	X			
Locator information	X	X	X	X
Demographic information		X		
Randomization		X		
HIV counseling	X	X	X	X
Offer condoms and lubricant	X	X	X	X
Baseline acceptability assessment		X		
Baseline behavioral assessment		X		
Adherence counseling/pill count (Pill count Week 2 and 4 only)		X	X	X

Appendix ID – Schedule of Procedures and Evaluations for Annual HIV Testing Visits

LoA #4, 14 Dec 2017:

- Note: This appendix was added to the protocol.

Appendix ID: Schedule of Procedures and Evaluations for Annual HIV Testing Visits

The procedures listed below are for the following participants:

- **Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will be asked to attend annual HIV testing visits until all participants complete Step 2 of the study.**
- **Participants in Step 2 who prematurely stop receiving injections for any reason other than HIV infection will transition to Step 3, complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual HIV testing visits until all participants complete Step 2 of the study.**

In both cases above, these participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study.

Procedure	Annual HIV Testing Visit
Locator information	X
Offer condoms and lubricant	X
HIV counseling (pre- and post-test)	X
Targeted history, con meds, physical exam	X
Blood collection	X
HIV testing	X
Plasma storage	X
DBS storage	X

REVISION #38, V2.0, 25 Jul 2018:

- Appendix ID: Schedule of Procedures and Evaluations for Annual ~~HIV Testing~~ Visits
The procedures listed below are for the following participants:
 - Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will be asked to attend annual ~~HIV testing~~ visits until all participants complete Step 2 of the study.
 - Participants in Step 2 who prematurely stop receiving injections for any reason other than HIV infection will transition to Step 3, complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual ~~HIV testing~~ visits until all participants complete Step 2 of the study.

In both cases above, these participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study.

Procedure	Annual HIV Testing Visit
Locator information	X
Offer condoms and lubricant	X
HIV counseling (pre- and post-test)	X
Targeted history, con meds, physical exam	X
Blood collection	X
HIV testing	X
Plasma storage	X
DBS storage	X

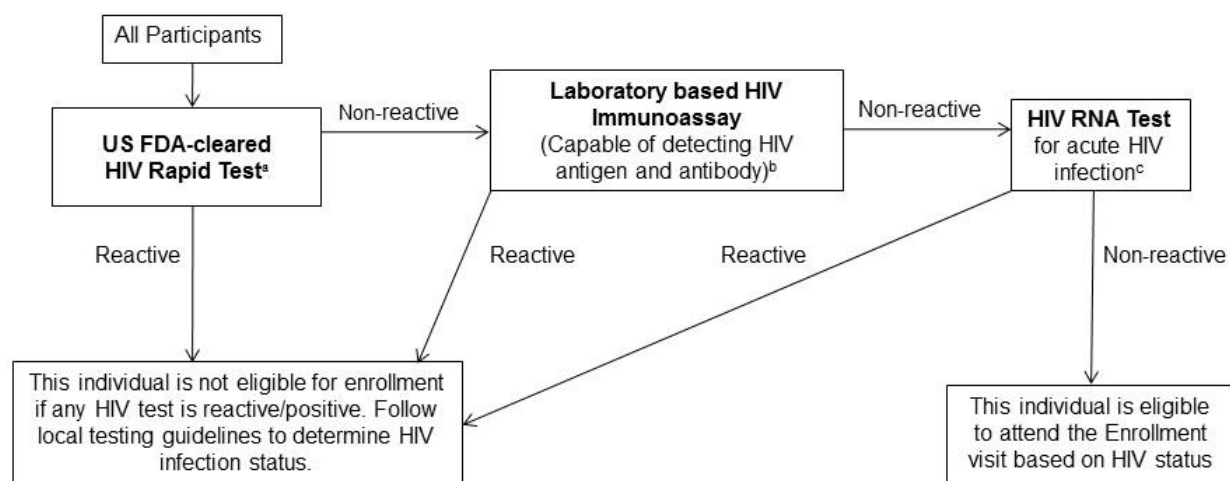
Appendix IE – HIV Testing Algorithm at the Screening Visit

LoA #4, 14 Dec 2017:

- Note: This appendix was added to the protocol.

Appendix IE: HIV Testing Algorithm at the Screening Visit:

HIV Testing Algorithm at Screening*



NOTES:

* Site-specific HIV testing plans must be approved by the HPTN LC before the study opens.

* Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

^b This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

^c Screening for acute infection should be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for this testing, such as the APTIMA HIV-1 RNA Qualitative Assay. RNA test results must be obtained from a specimen collected within 14 days prior to enrollment.

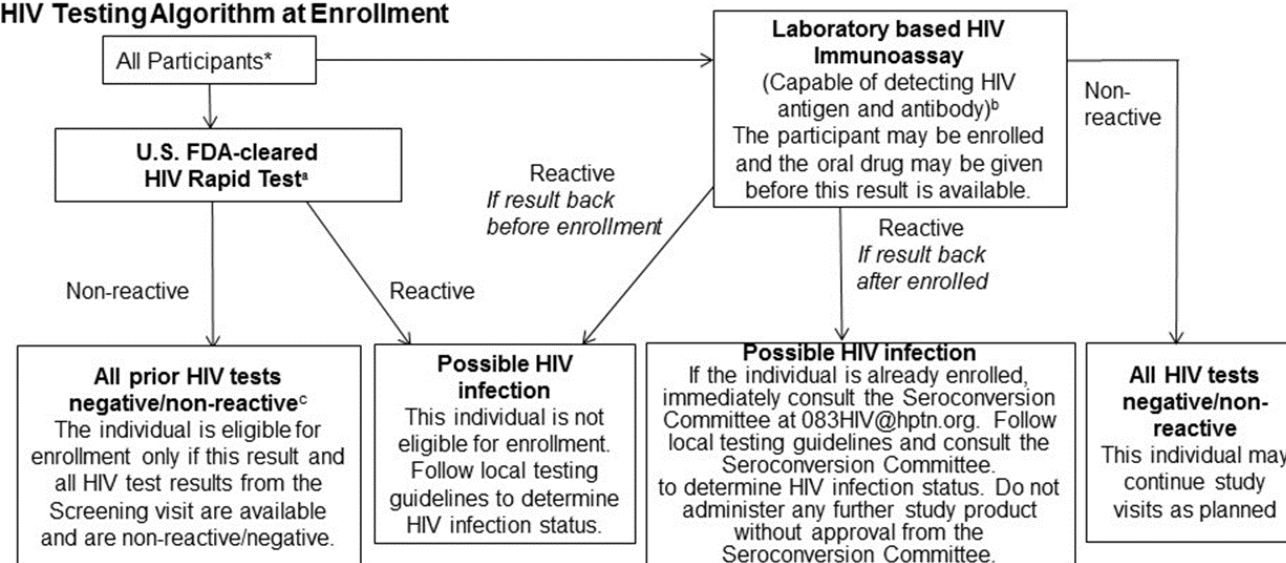
Appendix IF – HIV Testing Algorithm at the Enrollment Visit

LoA #4, 14 Dec 2017:

- Note: This appendix was added to the protocol.

Appendix IF: HIV Testing Algorithm at the Enrollment Visit:

HIV Testing Algorithm at Enrollment



NOTES:

* If acute HIV infection is suspected, do not enroll the participant or administer study product at this time. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

^a Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

^b This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

^c Before providing study drug, the site must ensure that the HIV rapid test from the Enrollment visit, and all HIV results from the Screening visit are available and are negative or non-reactive.

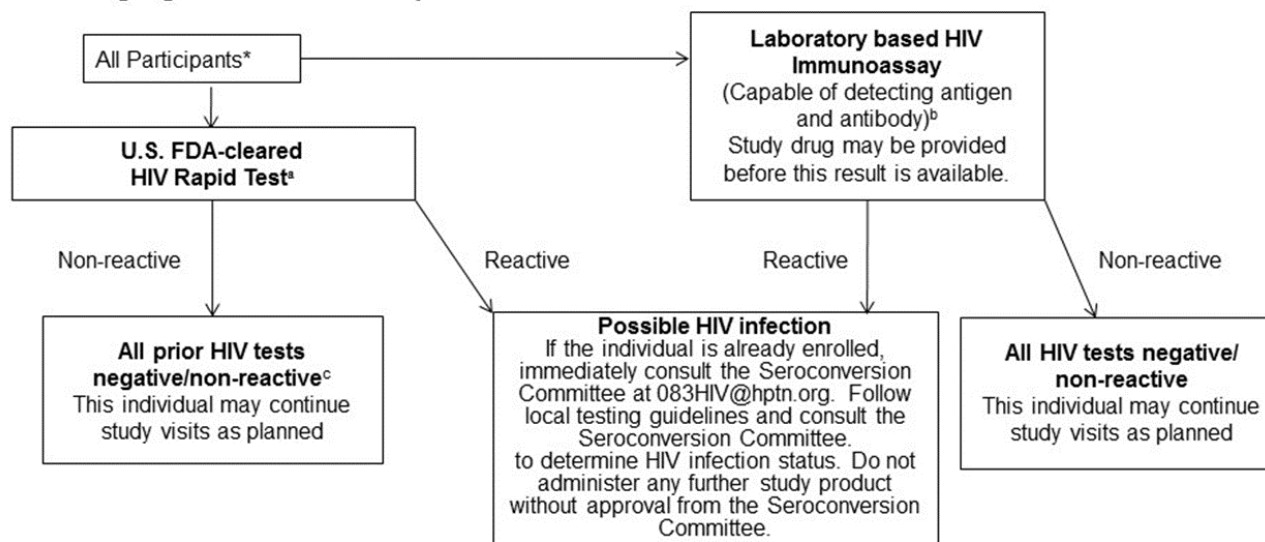
Appendix IG – HIV Testing Algorithm at Follow-up Visit:

LoA #4, 14 Dec 2017:

- Note: This appendix was added to the protocol.

Appendix IG: HIV Testing Algorithm at Follow-up Visit:

HIV Testing Algorithm for Follow up Visits



NOTES:

*If acute HIV infection is suspected, do not administer any further study product. Immediately consult the Seroconversion Committee. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

^a Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

^b This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

^c At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive.

Appendix II – Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

LoA #3, 10 Nov 2016:

- Only the note included in this appendix is depicted below.

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who become infected at any time during the study. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Step 2 of the study. Participants with confirmed HIV infection in Step 3 of the study may undergo similar procedures as listed in Weeks 12, 24, 26, and 48, and will be determined by the members of 083HIV@hptn.org CMC.

LoA #4, 14 Dec 2017:

- The following note was added under Note 1 in the appendix.

Note 2: Procedures for discordant or discrepant HIV test results are outlined in the SSP.

LoA #1, 24 May 2016:

- Note: Only the relevant section of the Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit) is depicted.

	HIV Confirmation Visit	Week 12	Week 24	Week 36	Week 48 ⁶
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Offer condoms and lubricant	X	X	X	X	X
HIV counseling	X				
CLINICAL EVALUATIONS AND PROCEDURES					
History, con meds, physical exam	X	X	X	X	X
Blood collection	X	X	X	X	X
LOCAL LABORATORY EVALUATIONS					
HIV testing ¹	X				
CD4 cell count	X		X		X
HIV viral load testing	X		X		X
HIV resistance testing ²	X				
Chemistry testing ³		X	X	X	X
Liver function testing ⁴		X	X	X	X
Plasma storage ⁵	X	X	X	X	X
DBS storage	X				

Appendix III – Toxicity Management

Toxicity Management General Guidance

LoA #2, 26 Jul 2016:

- Note: The second and third paragraphs of this section are impacted and included below.

The following general guidance refers to all AEs except for ~~AST/ALT~~. Refer ~~to the section below “Specific Guidance on Transitioning from Oral to Injectable Phase”, as well as~~ to the table below for specific guidance for ALT.

Grade 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed in the Table below may continue use of the study product per protocol. ~~See an exception to this under “Specific Guidance on Transitioning from Oral to Injectable Phase”.~~

LoA #4, 14 Dec 2017:

- Note: The fourth paragraph of this section is impacted and included below.

Grade 3

Participants who develop a Grade 3 AE or toxicity that is not specifically addressed in the Table below and is judged to be related to study product by the Investigator, study product use should be temporarily discontinued in consultation with the CMC. In general, and unless otherwise decided in consultation with the CMC, the investigator should re-evaluate the participant until resolution of the toxicity. For Grade 3 AEs deemed related to study product, the study product should be permanently discontinued if improvement to severity \leq Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed and the same Grade 3 AE recurs at any time, the Investigator must consult the CMC for further guidance on holding of study product, frequency of reevaluation or progression to permanent discontinuation of the study product. For Grade 3 AEs deemed unrelated to study product, the CMC should be consulted for further management recommendations. **Additionally, for Grade 3 or higher abnormalities at Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration.**

REVISION #39a, V2.0, 25 Jul 2018:

- In general, the IoR has the discretion to hold study product at any time if she/he feels that continued product use would be harmful to the participant, or interfere with treatment deemed clinically necessary according to the judgment of the IoR. In addition, a Clinical Management Committee (CMC) will be established for this study. The CMC’s responsibilities will include consultation and decision-making regarding management of toxicities and study product administration, including product resumption following the occurrence of certain types of toxicities and/or permanent discontinuation. Throughout this appendix are examples of AEs that require consultation with the CMC; in all such cases, the CMC should be notified as soon as possible and ideally within 72 hours of site

awareness of the AE in question. Investigators also should consult the CMC for further guidance in restarting study product or progressing to permanent discontinuation. Revealing a participant's blinded status will occur only for individuals who become HIV infected and choose to initiate antiretroviral therapy, **or in the case of a medical management decision (as approved by DAIDS), or as outlined in Section 5.12.1 of the protocol and Appendix VI of the SSP regarding unblinding in the event of an immediate medical emergency.**

The following general guidance refers to all AEs except for ALT, **creatinine clearance (absolute and change from baseline), and CPK. Refer to the tables below for specific guidance about these laboratory abnormalities.** ~~Refer to the table below for specific guidance for ALT.~~

Grade 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed in the Table below may continue use of the study product per protocol.

Grade 3

Any grade 3 or higher clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing. Participants who develop a Grade 3 AE or toxicity that is not specifically addressed in the Table below and is judged to be related to study product by the Investigator, study product use should be temporarily discontinued in consultation with the CMC. In general, and unless otherwise decided in consultation with the CMC, the investigator should re-evaluate the participant until resolution of the toxicity. For Grade 3 AEs deemed related to study product, the study product should be permanently discontinued if improvement to severity \leq Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed and the same Grade 3 AE recurs at any time, the Investigator must consult the CMC for further guidance on holding of study product, frequency of reevaluation or progression to permanent discontinuation of the study product. For Grade 3 AEs deemed unrelated to study product, the CMC should be consulted for further management recommendations. Additionally, for Grade 3 or higher abnormalities at Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration.

Grade 4

Any grade 4 or higher clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing. Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study product) should have the study product temporarily discontinued. The Investigator must consult the CMC and continue the temporary study product hold until a recommendation is obtained from the CMC. In general, study product use will not be resumed if the Grade 4 AE is considered related to study product use. If, in consultation with the CMC, study product use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study product must then be permanently discontinued.

General Criteria for Discontinuation of Study Product

LoA #4, 14 Dec 2017:

- Note: The last paragraph has been revised and is included below.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually for HIV testing ~~only~~ until ~~the~~ **all participants complete conclusion** of Step 2 of the study. All such cases must be reported to the CMC.

REVISION #39b, V2.0, 25 Jul 2018:

- The last paragraph is impacted and included below.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually ~~for HIV testing~~ until all participants complete Step 2 of the study. All such cases must be reported to the CMC.

Guidance on Toxicity Management for Specified Toxicities: ALT

REVISION #39c, V2.0, 25 Jul 2018:

CONDITION AND SEVERITY ¹	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT ²
ELEVATIONS in ALT		
Grade 2 and higher		<p>Oral phase: A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is \leq Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is $<$ Grade 2 at Week 4, the participant may proceed to Step 2 injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually for HIV testing only until all participants complete Step 2 of the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1.</p> <p>A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually for HIV testing only until the conclusion of all participants complete Step 2 of the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1.</p> <p>Excluding ALT, any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.</p> <p>Grade 3 adverse events deemed related to study product, or a Grade 3 ALT, or any Grade 4 adverse event will lead to permanent study product discontinuation, and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study. AEs will be followed until resolution (\leq grade 1) in consultation with the CMC.</p> <p>Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually for HIV testing only until the conclusion of all participants complete Step 2 of the study. All such cases must be reported to the CMC.</p>

CONDITION AND SEVERITY ¹	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT ²
ELEVATIONS in ALT		
Grade 2 and higher		<p>Injection phase: The CMC should be notified as soon as possible. For a Grade 2 ALT, the CMC will determine whether further injections may be given in cases where levels are \leq Grade 2 prior to the next scheduled injection. Unless otherwise specified by the CMC, for Grade 2 ALT, repeat testing should be performed weekly until levels are \leq Grade 1. For Grade 3 and higher ALT, study product will be permanently discontinued-*. For Grade 3 and 4 ALT, repeat testing should be performed as soon as possible, and participants should be followed weekly until levels are \leq Grade 1. Participants who are permanently discontinued from study product should continue to be followed on study/off study product, following the Step 3 Schedule of Evaluations for Arm A. Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product. If the participant is in Step 1 of the study when this occurs, study product will be discontinued and the participant will be followed annually for HIV testing only until the conclusion of all participants complete Step 2 of the study. If the participant is in Step 2 when this occurs, the participant will transition to Step 3, off study product, and follow the Schedule of Procedures and Evaluations for Step 3 except for provision of study product. When Step 3 concludes in these cases, the participant will be followed annually until all participants complete Step 2 of the study. All such cases must be reported to the CMC.</p>

REVISION #39d, V2.0, 25 Jul 2018:

Creatinine Clearance

NOTE: Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF. Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should follow the “Toxicity Management General Guidance” ONLY when the absolute creatinine clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that DO NOT result in an absolute creatinine clearance < 90 mL/min do NOT need to be reported to the CMC or more frequent clinical monitoring.

CONDITION AND SEVERITY	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT
CREATININE CLEARANCE		
Estimated CrCl< 60 mL/min	Discontinue study product temporarily	If the calculated creatinine clearance is <60mL/min, it should be confirmed within 1 week of the receipt of the results, and the CMC should be consulted for adjudication and recommendation for further testing and follow-up.
Confirmed CrCl< 60 mL/min	Permanently discontinue study product	If the calculated creatinine clearance is confirmed to be <60 mL/min, the study product must be permanently discontinued and the CMC notified. Participants who fail to have a confirmed test within 2 weeks of receiving the initial result, should be discontinued from use of the study product until CMC adjudication and recommendation for further testing and follow-up.
Re-testing result is ≥60 mL/min	Consult CMC for guidance	If re-testing yields a result ≥ 60 mL/min, the Investigator must consult the CMC for further guidance on resuming study product use, continuing the hold temporarily, or progressing to permanent discontinuation. If the investigator in consultation with the CMC has determined that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study product.

Guidance on Toxicity Management for Specified Toxicities: Creatine Phosphokinase (CK or CPK)

LoA #4, 14 Dec 2017:

CONDITION AND SEVERITY ¹	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT
Creatine Phosphokinase		
Grade 3	Continue study product until repeat test results are available	A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of products known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.
Grade 4	Continue study product until repeat test results are available if the elevation is thought to be possibly or probably related to study product.	Grade 4 elevations in CPK should have a repeat assessment within 2 weeks at least 24 hours after the subject has abstained from exercise for >24 hours . For persistent Grade 4 CPK elevations that are symptomatic (myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance, defined in consultation with the CMC) should have study product discontinued. Otherwise, the CMC will provide guidance on frequency of additional CPK monitoring. considered possibly or probably related to the study product, study product should be discontinued and the participant should be followed on study/off study product.

Guidance on Toxicity Management for Specified Toxicities: Creatine Phosphokinase (CK or CPK)

REVISION #39e, V2.0, 25 Jul 2018:

CONDITION AND SEVERITY ¹	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT
Creatine Phosphokinase		
Grade 1 and 2	Continue study product	A Grade 2 or lower elevation does not warrant retesting or changes to study product use.
Grade 3	Continue study product until repeat test results are available	A Grade 3 or higher elevation in CPK should result in a repeat assessment within 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of products known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained. If after retesting, a Grade 3 elevation persists, consult the CMC for guidance.
Grade 4	Continue study product until repeat test results are available if the elevation is thought to be possibly or probably related to study product.	Grade 4 elevations in CPK should have a repeat assessment within 2 weeks at least 24 hours after the subject has abstained from exercise. For persistent Grade 4 CPK elevations that are symptomatic (myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance, defined in consultation with the CMC) should have study product discontinued. Otherwise, the CMC will provide guidance on frequency of additional CPK monitoring and ongoing study product use.

Guidance on Toxicity Management for Specified Toxicities: QTc – Criteria for Permanent Discontinuation of Study Product

LoA #1, 24 May 2016:

- A participant that meets either criterion below will have study product stopped, but will remain in study follow-up. The QT (**QTc**) correction formula used to determine study product discontinuation should be the same one used throughout the study. **For example, either Bazett's (QTcB) or Fridericia (QTcF) correction formula may be used, as long as the same formula is used throughout for a given participant.**
 - QTcB > 550 msec, OR
 - Change from baseline: QTcB > 60 msec

Appendix IV: Sample Screening and Enrollment Informed Consent Form

REVISION #40a, V2.0, 25 Jul 2018:

- The first page of the sample consent form is updated to reflect Version 2.0, dated July 25, 2018.

Study Groups

LoA #1, 24 May 2016:

- Note: Only the relevant section of the sample consent form is depicted below.

Group A – this group gets real CAB pills and injections:

- Step 1: Real CAB pill AND placebo pill for TDF/FTC (2 pills total) every day for 5 weeks
- Step 2: Real CAB injections given as one shot, then another shot a month later, and then every 2 months after that AND placebo pill for TDF/FTC every day up to ~~four~~ **three** and half years
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

Group B – this group gets real TDF/FTC pills:

- Step 1: Real TDF/FTC pill AND placebo pill for CAB (2 pills total) every day for 5 weeks
- Step 2: Placebo CAB injection AND real TDF/FTC pill everyday up to ~~four~~ **three** and a half years
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

LoA #2, 26 Jul 2016:

- Note: Only the relevant section of the sample consent form is depicted below.

In Step 1, everyone starts the study by taking pills for 5 weeks. This is to see if you have any serious side effects to the study drugs before you start getting the shots.

In Step 2, everyone takes pills and gets shots. This step will last up to ~~four~~ **three** and a half years, depending on when you started in the study.

In Step 3, everyone gets the real TDF/FTC every day for about a year, then your participation in the study will end and we will refer you to local HIV prevention services. There are no current plans for the study to offer the injectable CAB drug to study participants after the completion of the study.

Study Procedures

LoA #1, 24 May 2016:

- Note: Only the relevant portion of the Screening Visit section of the consent form is depicted.

Your screening visit may occur after you read, discuss, understand, and sign this form, or will we schedule it for you at another time. We will help you understand the form and answer your questions before you sign this form. The procedures done for the screening visit will take about *[site to fill in time required]*, and may be done at one or more visits.

At this visit, the study staff will:

- Ask you where you live and other questions about you, your medical health, your sexual practices, including if you are at a higher risk of getting HIV, and whether you use alcohol or drugs. ***[Sites in US to add this here: We will ask you to answer some additional questions about sexual practices using an assessment called SexPro, which may provide additional information about your HIV risk, and whether this study is appropriate for you.] [Sites in South America to add this here: We will ask you to answer some additional questions about sexual practices using an assessment called SexPro, which may provide additional information about your HIV risk.]***
- Give you a brief physical exam to make sure you are healthy.
- Talk with you about HIV and ways to protect yourself from getting it and offer condoms and lubricant.
- Have an electrocardiogram (ECG) scan, which is a test to monitor your heart.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, Hepatitis B and C testing, to check your general health, to check the health of your liver, and for storage for study-related testing.
- *[Sites participating in the DXA substudy to include this:]* We may ask you to be a part of a group that gets bone mineral density-energy x-ray absorptimetry (DXA)

scans. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. **We know that TDF/FTC may cause thinning or softening of bones in some people. We want to see whether there are changes to your bones during the study, and the DXA scan lets us evaluate your bones. We want to see if this is different between the TDF/FTC and CAB treatments.** The scan will be done at the Enrollment visit (this visit), and 2 other times during the study (Weeks 57 and 105).

LoA #2, 26 Jul 2016:

- Note: The last bullet under Screening Visit is impacted by this change and depicted below.
 - *[Sites participating in the DXA substudy to include this:]* We may ask you to be a part of a group that gets a bone mineral density-energy x-ray absorptimetry (DXA) scan. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. We know that TDF/FTC may cause thinning or softening of bones in some people. We want to see whether there are changes to your bones during the study, and the DXA scan lets us evaluate your bones. We want to see if this is different between the TDF/FTC and CAB treatments. The scan will be done at the Enrollment visit (this visit), and 2 other times during the study (Weeks 57 and 105). **The results of the DXA scans will be given to you at the end of the study.**

LoA #1, 24 May 2016:

- Note: Only the relevant portion under the Confirmation of Eligibility section of the consent form is depicted.

Once all the results of the screening tests are known, the following will happen within 45 days after screening:

- You will be told your test results and what they mean.
- If you have a positive HIV, hepatitis B or C test you will not be eligible for the study, and you will be referred for the appropriate medical care (*sites to add specifics about this here as necessary*).
- If you are negative for HIV but the results from the other blood ~~or urine~~ tests show that you might have some health problems, you may not be eligible for the study. Study staff will refer you to available sources of medical care and other services you may need. Later, if these problems resolve, you may be able to come back to find out if you are eligible at that time.

REVISION #40b, V2.0, 25 Jul 2018:

- Note: Only the relevant portion under Step 1: Enrollment Visit is included below.
 - We may ask you to be a part of a group that gets a bone mineral density-energy x-ray absorptimetry (DXA) scan. A DXA scan is a special kind of x-ray using a

small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. **The subset will include 350 participants.** The scan will be done at the Enrollment visit (~~this visit~~), and 2 other times during the study (Weeks 57 and 105). ~~[Sites that do not participate in the DXA subset to delete this]~~. If you are in this group, we will also check your blood to see how much Vitamin D is in it, **and will ask you about your diet to see if you are eating foods with calcium in it. We will tell you if the DXA subset is no longer available to participate in.** ~~[Sites that do not participate in the DXA subset to delete this entire bullet item].~~

REVISION #40c, V2.0, 25 Jul 2018:

- Note: This paragraph is added after the bulleted items at the bottom of Step 1: Weeks 2 and 4 Visits.

If you have a side effect from the pills, or if you do not take enough of your pills, you may not be able to get the shots. If this happens, we will ask you to attend a visit once a year until all participants in the study have completed Step 2. The procedures for those visits are outlined later in this consent form document [sites may also list the procedures here].

LoA #4, 14 Dec 2017:

- Note: The following paragraph has been added just below the last bullet and before the last paragraph under Step 3.

It may be necessary for additional visit(s) and procedures in the event of unforeseen or unanticipated results; for example, you may have a side effect that requires repeat testing on your blood to ensure that the study drugs continue to be safe for you to use. Or, sometimes the results of some tests are not clear and additional testing is needed in order to confirm a test result. There also may be difficulties in sample shipping, processing, or testing; and/or if you are experiencing any symptoms or changes in your physical condition. In the event of any of these unforeseen or unanticipated results, we will explain to you what will happen and what procedures will need to be done.

REVISION #40d, V2.0, 25 Jul 2018:

- Note: Only the relevant portion of Step 3 is included below.
 - Give you a brief physical exam, **and ask you about any other medicines you are taking**
 - Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing, to check your general health, the health of your liver, the amount of the study drug in your blood, and for storage. **Note: Blood will be collected for syphilis testing at Day 0, and Weeks 24 and 48. However, if you have had syphilis testing within 3 months of joining this part of the study, you will only have this done at Week 24 and Week 48.**

REVISION #40e, V2.0, 25 Jul 2018:

- Note: The first paragraph just below the last bullet under Step 3 is impacted and included below.

It may be necessary for additional visit(s) and procedures in the event of unforeseen or unanticipated **events or** results; for example, you may have a side effect that requires repeat testing on your blood to ensure that the study drugs continue to be safe for you to use. Or, sometimes the results of some tests are not clear and additional testing is needed in order to confirm a test result. There also may be difficulties in sample shipping, processing, or testing; and/or if you are experiencing any symptoms or changes in your physical condition. **There also may be a time that you are not able to complete all of the procedures in a visit and you have to come back the next day or another day, and additional blood may be needed when you come back in order to complete the requirements of the visit.** In the event of any of these unforeseen or unanticipated results, we will explain to you what will happen and what procedures will need to be done.

REVISION #40f, V2.0, 25 Jul 2018:

- Note: This section now labeled “Annual Visits” is after Step 3 and before Procedures if you become infected with HIV during the study.

Annual Visits

Procedures for HIV testing every year if you do not get shots or have completed or been in Step 3:

As we mentioned, the study begins with taking pills only for five weeks before you can start with the shots. During this time, you may get a side effect that would result in not moving to the part of the study where the shots are given. ~~If~~**Or, you may not have taken enough of the pills. If any of** this happens, you would not get shots, and we would ask you to attend a visit once a year while Step 2 of the study is still ongoing in order to test you for HIV.

If you do get shots but stop getting them early, you will move to Step 3 of the study where you will get real TDF/FTC for approximately a year and come in for visits every three months for approximately a year. After that time, we will help you find prevention services in the local area, and we will ask you to attend a visit once a year while Step 2 of the study is still ongoing in order to test you for HIV.

The procedures for these visits every year while Step 2 of the study is still ongoing are:

- Confirm where you live and how to contact you.
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a brief physical exam., **and ask you about any medicines you are taking.**
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, the amount of the study drug in your blood, and for storage.

- Give you condoms and lubricant.

LoA #4, 14 Dec 2017:

- The section below appears after the description of procedures for Step 3, and before the section called “If you become infected with HIV during the study”.

Procedures for HIV testing every year if you do not get shots or have completed or been in Step 3:

As we mentioned, the study begins with taking pills only for five weeks before you can start with the shots. During this time, you may get a side effect that would result in not moving to the part of the study where the shots are given. If this happens, you would not get shots, and we would ask you to attend a visit once a year while Step 2 of the study is still ongoing in order to test you for HIV.

If you do get shots but stop getting them early, you will move to Step 3 of the study where you will get real TDF/FTC for approximately a year and come in for visits every three months for approximately a year. After that time, we will help you find prevention services in the local area, and we will ask you to attend a visit once a year while Step 2 of the study is still ongoing in order to test you for HIV.

The procedures for these visits every year while Step 2 of the study is still ongoing are:

- **Confirm where you live and how to contact you.**
- **Talk with you about HIV and ways to protect yourself from getting it.**
- **Give you a brief physical exam.**
- **Collect ~XX mL (about x teaspoons) of blood for HIV testing, the amount of the study drug in your blood, and for storage.**
- **Give you condoms and lubricant.**

Risks and/or Discomforts

LoA #4, 14 Dec 2017:

- Note: The first paragraph of this section is impacted and depicted below.

Study Medications

The side effects of cabotegravir include:

~~Headaches, diarrhea, and fatigue. With the CAB that you get as a shot, people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising where they got the shot. Other reported side effects include muscle aches, nausea, fever and dizziness.~~

- Headache
- Diarrhea

- Fatigue
- Muscle aches
- Nausea
- Fever
- Dizziness
- **Runny nose**
- **Sore throat**
- **Upper respiratory tract infection**
- **Vomiting (being sick)**
- **Difficulty sleeping**
- **Abnormal dreams/nightmares**
- **Depression**
- **Flatulence (gas or wind)**
- **Increase in the level of enzymes in the muscles (creatine phosphokinase)**
- With the CAB that you get as a shot, **some** people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising in the area where they got the shot, **some of which lasted a few weeks before resolving.**

LoA #2, 26 Jul 2016:

- Note: The second paragraph under “The side effects of cabotegravir include:” is impacted by this change and depicted below.

There have been some people who were taking this medicine ~~in other studies~~ who have had liver side effects. ~~Most~~ **Some** of these people were HIV-infected (HIV positive) and ~~they all had~~ some ~~had~~ damage to their liver before taking the CAB study medication. ~~In those studies, w~~ While taking the study medication, their blood tests showed that their liver was irritated, although they felt well. The medications were stopped, and the liver blood tests ~~are~~ **returned to** normal. In this study, anyone with HIV-infection, Hepatitis C (or B), or any liver irritation will not be allowed to be in the study.

LoA #3, 10 Nov 2016:

- Note: The fourth paragraph under “The side effects of cabotegravir include:” is impacted and depicted below.

The shots you receive in this study are long acting, meaning they stay in your body for a long time – **as long as a year or more.** ~~One single shot can stay in your body for up to one year.~~ If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you are in Group A, the group that gets the real CAB, we will monitor your health for a year after your last injection. If you get infected with HIV while on the real CAB, it is possible that real CAB and other HIV drugs that are like it may not work to fight the virus.

LoA #1, 24 May 2016:

- Note: Only the relevant portion under “Side effects of TDF/FTC include:” is depicted below.

Side effects of TDF/FTC include:

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Other side effects include:

~~The following side effects have been associated with the use of tenofovir:~~

- Upset stomach (nausea), vomiting, gas, loose or watery stools
- Abdominal pain
- Generalized weakness
- Dizziness
- Depression
- Headache
- Shortness of breath
- Increased ~~cough~~ **cough**
- Runny nose
- Allergic reaction: symptoms may include fever, rash, itching, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue.
- Skin darkening of the palms of hands and/or soles (bottom) of feet
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage (**this side effect goes away after stopping TDF/FTC**)

LoA #1, 24 May 2016:

- Note: Only the new paragraph is depicted below, and is placed directly after “Side effects of TDF/FTC include:” and before “Blood Draws.”

Side effects of Intralipid when used as an intramuscular injection placebo include headache, anxiety, insomnia, vomiting, nausea, constipation, extremity pain, agitation, diarrhea, sedation, nasopharyngitis, upper respiratory infection, cough, urinary tract infection, decreased weight, and increased muscle tone.

When Intralipid is given as an intravenous infusion (into a vein directly) for nutrition, the following side effects have been reported (note that these side effects have not been reported when Intralipid is administered through an intramuscular injection):

Immediate or early adverse reactions, each of which has been reported to occur in clinical trials less than 1% of the time: trouble breathing, blue appearance to the skin at where the injection was given, allergic reactions, elevated levels of fat in your blood, increased chances of getting blood clots, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, and irritation at the site of the infusion;

Delayed adverse reactions such as: large liver, yellowing of the skin and eyes, large spleen, low blood cell counts, increases in liver function tests, and overloading syndrome (seizures, fever, increase in white blood count, large liver, large spleen, and shock).

LoA #3, 10 Nov 2016:

- Note: The “HIV Infection” section is impacted and depicted below.

HIV Infection

We told you earlier that we do not know if CAB works to protect you from getting HIV. If you are in the group that gets the real CAB, you still may be at risk of getting HIV. We do know that taking TDF/FTC every day can be very effective at preventing HIV infection. If it is not taken every day, you may not be well protected. Because of these risks, it is very important that you use condoms every time you have sex, no matter what group you are in.

Because the study medication is itself being studied to be an HIV treatment medication, if you become HIV infected while taking the study medication, there is a chance that other drugs used to treat HIV infection might not work. This is called drug resistance.

To reduce the possibility of developing drug resistance, you will be asked to work with your local study clinic team to begin HIV treatment after your last study medication injection. The study will not provide this treatment but may be able to help you find and/or pay for that treatment.

Confidentiality

LoA #4, 14 Dec 2017:

- Note: Only the relevant portion under “Confidentiality” is depicted below.

Your records may be reviewed by:

- US FDA
- US NIH

- US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs/ECs/other local review bodies as applicable]
- Study staff
- Study monitors
- Companies that make the study drug (ViiV Healthcare and Gilead Sciences, Inc.)
- **Other U.S., local, and international regulatory entities may also review study records**

Signature Page

REVISION #40g, V2.0, 25 Jul 2018:

- Note: The signature page is updated to reflect Version 2.0, dated July 25, 2018. An addition to the list of items to be initialed by participants is included below.

_____ ***[Sites that are participating in the DXA subset to add this]: I have been told that the DXA subset is no longer available for participation.***